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DOCTORAL THESIS

Evaluation of Effectiveness of Risk Minimisation Measures in Europe

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I dedicate this thesis to my family and friends.

I am truly thankful for having you all in my life.

Abstract

Background: Therapeutic Risk Minimisation (RM) has become as an area of extensive research in recent years with the release of Good Pharmacovigilance Practice Module XVI in 2014 which provides a regulatory framework for selection, development and evaluation of the effectiveness of additional risk minimisation measures (aRMMs) in Europe. Over a quarter of new products currently approved centrally by the European Medicines Agency (EMA) have accompanying aRMMs to manage and mitigate risks that could have serious consequences for patients and are considered to be insufficiently managed by routine measures alone. Most of these aRMMs are educational and communication materials for healthcare professionals (HCPs) or patients such as brochures, leaflets, guides, checklists, Direct HCP Communications (DHPCs), patient cards, pregnancy prevention programmes (PPPs). Safety concerns addressed by aRMMs range from adverse reactions associated with the drug to medication and administration errors, or the increased risk in special populations such as pregnant women.

Efforts are being made in Europe to evaluate the effectiveness and implementation of aRMMs, to establish whether an intervention has been effective, and, if not, why and which corrective actions are necessary. The effectiveness of aRMMs may be assessed through process indicators (e.g. receipt, use, knowledge, self-reported behaviour, mainly via survey studies), behavioural changes (e.g. drug utilization studies) and/or health/safety outcomes (e.g. rates of adverse events). The term risk minimisation evaluation (hereinafter '*RMEv*') is used in this document to describe a study or group of studies that assess the effectiveness of aRMMs for one specific product. Studies linked to one product are considered part of the product RMEv. RMEv should ideally include measures of effectiveness at the three levels of evaluation: process indicators, behavioural outcomes, and health/safety outcomes. However, this may vary by product.

This thesis evaluates subject participation, country selection, study results and regulatory consequences of survey studies evaluating the effectiveness of aRMMs via process indicators in Europe (hereinafter *EU RM Surveys*). Additionally, this thesis describes RMEv which include process indicators and outcomes and provides a potential methodological framework for RMEv at the three evaluation levels (process indicators, behavioural outcomes, and health/safety outcomes) via a non-interventional post-authorisation safety study (PASS) with results endorsed by EMA regulators. The study was conducted to evaluate the effectiveness of the abatacept (ORENCIA®) patient alert cards (PACs) in rheumatoid arthritis (RA) patients and HCPs. Two PACs are available, one for each formulation (intravenous [IV] and subcutaneous [SC]), to help inform patients and HCPs of the potential risks and actions required during treatment with the product, specifically for infections and allergic reactions, with the ultimate goal of reducing the occurrence of undesirable outcomes (e.g., hospitalisations), or severity (e.g., reducing delays in seeking medical care).

Methods: We conducted a systematic literature review in the EU PAS Register, PubMed and grey literature to search for study reports and manuscripts of completed EU RM Surveys between Jan 2011 and Jan 2018. Regulatory consequences/actions were extracted from Assessment Reports of study results issued by competent authorities. Random effects models to combine proportions were used for: participation rates (i.e. proportion of subjects invited who completed the survey; proportion of subjects eligible who completed the survey), receipt (i.e. proportion of participants who reported having received the materials), reading (i.e. proportion of participants who reported having read the materials among those who received them), use (i.e. proportion of participants who reported having used the materials among those who received them), and knowledge (i.e. proportion of participants who correctly responded the knowledge questions).

The search was updated in October 2019 using the EU PAS Register, PubMed, and grey literature to capture a greater number of EU RM Surveys. Studies identified were used to extract more detailed data on country selection and subject participation overall and by country. This allowed to calculate: number and percentage of studies in which each country participated, number and percentage of completers that each country provided, by study and overall: 1) as the percentage of completers each country provided to the overall number of completers in all studies; or 2) as the percentage of completers each country provided to the overall number of completers in studies with that country participation identified. Response rate was calculated as the percentage of participants who completed the survey among those invited to participate. The range of response rates was described.

As part of the search conducted in October 2019 studies to assess the effectiveness of aRMMs (hereinafter *EU RM studies*) using behavioural and/or health/safety outcomes were also retrieved. Identified studies linked to one product were assigned to the product RMEv. Only RMEv that included both process indicators and outcomes (behavioural and/or health/safety outcomes) were reviewed. Data were extracted which included: at RMEv level (ATC group, type of aRMM, targeted safety concerns, number of studies conforming the RMEv i.e., 1 study, 2 studies or ≥3 studies) and at study level (study design, countries, outcome measures, data sources). Where available study results were obtained and summarised.

A PASS study evaluating the effectiveness of abatacept PACs and consisting of three sub-studies was carried out in five European countries: 1) survey of HCPs (nurses and physicians), 2) survey of patients, and 3) retrospective chart review in the same patients who completed the survey. This permitted linking clinical and safety outcomes obtained via the chart review with survey responses in the same patients. Survey responses were analysed descriptively, and summary scores for endpoints (scores of utility, utilisation, knowledge, behaviour, and global score) were calculated. All analyses were performed overall and by receipt versus non-receipt of the PACs.

The study assessed whether better responses provided by abatacept-treated patients in the patient survey were associated with improved outcomes (e.g. availability of results of screening tests for tuberculosis (TB) and viral hepatitis (VH) prior to abatacept use, occurrence of infections leading to hospitalisation and/or infections leading to emergency room visits and time from occurrence of infection to receiving medical attention). Univariate analyses correlated within-patient clinical and safety outcomes responses to process indicators in the patient survey.

For all the analyses, differences between groups were assessed using parametric and non-parametric statistical methods as applicable. *P*-values < 0.05 were considered statistically significant.

Results: In the initial search conducted in January 2018, 109 EU RM studies were identified, of which 24 had a survey component and results available at the time of the analysis. Of these, 23 studies targeted HCPs. The pre-specified sample size was reached in 52% of studies. The pooled HCP participation was 5% defined as completers/invited and 89% for completers/eligible. Receipt of materials was recalled by 60% of HCPs and 77% of items scored knowledge >60%. Eight studies targeted patients/caregivers. The pre-specified sample size was reached in only two. The pooled participation was 93%, defined as completers/eligible. Materials were received by 50–80% of patients and read by over 90%. Patients only scored knowledge >60% in 38% of items. Further action was requested by regulators in 59% of studies.

In the updated search conducted in October 2019, of 129 EU RM studies, the number of completed surveys raised up to 48. Twenty-eight different European countries participated in the 44 surveys that targeted HCPs (mean: 6 countries per study). UK, Spain, France and Germany were the most frequently selected countries, contributing 64% of all participants with country-specific data. Seventeen different European countries participated in the 14 surveys that targeted patients/caregivers (mean: 5 countries per study). UK, Germany, France and Spain were the most frequently selected countries, contributing 66% of all participants with country-specific data.

In the search of October 2019, 102 product-specific RMEv were identified, of which 18 (18%) had both process indicators and outcomes. Of the 18 RMEv, ten consisted of one study only, five of two studies, and three of three or more studies. A total of 30 studies were included within the 18 RMEv. The designs of the studies were: 19 (63%) cross-sectional surveys (47% targeted patients and 89% healthcare professionals), 17 (57%) retrospective studies (47% using pre/post approach) and 3 (10%) prospective studies. Nineteen studies included process indicators that were receipt (n=14), use (n=12), knowledge (n=17) and self-reported behaviour (n=15). Regarding outcomes, 67% of the 18 RMEv evaluated behavioural outcomes and 50% health/safety outcomes. Three of the 18 RMEv evaluated both behavioural and health/safety outcomes. For five RMEv, correlations between process indicators and outcomes were performed, two at the patient level. Results were available for 14 of the 18 RMEv. In HCP surveys, the median percentage was 57% for receipt, 92% for reading, 80% for use, 77% for

knowledge and 74% for behaviour. In patient surveys, the median percentage was 56% for receipt, 87% for reading, 65% for use, 47% for knowledge and 69% for behaviour. Knowledge was better in healthcare professionals than patients ($p < 0.05$). Three of the 5 RMEv which included a correlation analysis had results available. Of these, only one (the abatacept study later described) found a positive trend for a lower occurrence of outcomes as process indicators improved, though this was not statistically significant.

In the abatacept case study, data on 190 patients and 79 HCPs (50 physicians and 29 nurses) were analysed. Sixty percent of patients were aware of the PAC, of whom 95% had received it. Knowledge of risk of infection was higher among patients who had received the PAC vs those who had not (64% vs 46%; $p = 0.013$). Infections leading to hospitalisation increased with decreasing patient survey global scores: scores of >67%, 34%-67% and ≤ 33% were associated with hospitalisation rates of 2.5%, 5.2% and 8.4%, respectively ($p = 0.4$). Among HCPs, 90% were aware and 68% had accessed the PAC. More nurses than physicians were aware (93% vs 88%), had accessed (78% vs 74%), read (90% vs 59%), distributed (81% vs 66%) and explained the content (94% vs 43%) of the PAC. Knowledge of risk of infection was higher among HCPs who had (91%) vs those who had not (73%) accessed/received the PAC ($p = 0.053$).

Conclusions: The field of therapeutic RM has become an area of intensive research since the implementation of GVP XVI. As of October 2019, at least 129 EU RM studies had been designed and conducted to assess the effectiveness of RMMs for 102 different products in Europe. About forty percent of EU RM Surveys provided evidence that supports the effectiveness of RMMs based on regulatory Assessment Reports. The remaining sixty percent of studies required further action for distribution strategies, re-distribution, and follow-up assessment, changes to existing materials, further data awaited and, in a minority, removal of the materials. However, this review identified some challenges that remain in the design, conduct, and reporting of survey studies, which may benefit from more detailed guidance, use of common definitions, standardization of reporting. Some of the limitations of cross-sectional study designs (i.e., surveys) may be overcome by drug utilisation and outcomes evaluations which have been used conjunctively with EU RM Surveys in eighteen percent of RMEv to supplement the results of process indicators. There are currently few studies correlating within-patient survey results with heath/safety outcomes. This thesis provided a potential framework for the evaluation of effectiveness of aRMMs via a case study involving surveys and a retrospective chart review to correlate process indicators and safety outcomes in the same patients. This novel study design bridges the gap of linking process indicators with outcomes at the individual-patient level and strengthens the clinical relevance of results from surveys. The results support the effectiveness of the abatacept PACs. The practical impact of this study resulted in no modifications to the content of the PACs or further evaluations being requested by EMA regulators. The learnings of this thesis may be

used by MAHs, academic groups and regulatory authorities to inform the design of future RMEv approaches combining process indicators and outcomes.

Main references that supported this Doctoral Thesis

This thesis is based on the following publications, which are cited in the text as the Roman ordinal numerical reference:

List of Manuscripts:

I. Artime E, Qizilbash N, Garrido-Estepa M, Vora P, Soriano-Gabarró M, Asiimwe A, et al. Are risk minimization measures for approved drugs in Europe effective? A systematic review. Expert Opin Drug Saf. 2019;18:443–54. doi: 10.1080/14740338.2019.1612875.

II. Artime E, Qizilbash N, Herruzo R, Garrido-Estepa M. Risk Minimisation Evaluation with Process Indicators and Behavioural or Health Outcomes in Europe: Systematic Review. Pharmaceut Med. 2020;34(6):387-400. doi: 10.1007/s40290-020-00361-w.

III. Artime E, Kahlon R, Méndez I, Kou T, Garrido-Estepa M, Qizilbash N. Linking process indicators and clinical/safety outcomes to assess the effectiveness of abatacept (ABATACEPT) patient alert cards in patients with rheumatoid arthritis. Pharmacoepidemiol Drug Saf. 2020;29:664–74. doi: 10.1002/pds.5012.

List of Abstracts:

I. Artime E, Qizilbash N, Herruzo R, Garrido-Estepa M. Process indicators and outcomes to assess the effectiveness of additional risk minimisation measures in Europe. Pharmacoepidemiol Drug Saf. 2020;29(Suppl. 3):3–634. doi: 10.1002/pds.5114 (Annex 1).

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Previous research conducted by the doctoral candidate in the Doctoral Thesis scientific area

List of Manuscripts

1. Artime E, Shui I, Mendez I, Tcherny-Lessenot S, D'Arbigny P, Alfaro N, et al. Pre/post effectiveness evaluation of updated additional risk minimisation measures for an orphan disease: Myozyme (alglucosidase alfa) Safety Information Packet. Pharmacoepidemiol Drug Saf 2020;29:103–10. doi: 0.1002/pds.4905
2. Vora P, Artime E, Soriano-Gabarró M, Qizilbash N, Singh V, Asiimwe A. A review of studies evaluating the effectiveness of risk minimization measures in Europe using the European Union electronic Register of Post-Authorization Studies. Pharmacoepidemiol Drug Saf 2018;1–12. doi: 10.1002/pds.4434
3. Rubino A, Artime E. A descriptive review of additional risk minimisation measures applied to EU centrally authorised medicines 2006-2015. Expert Opin Drug Saf 2017;16:877–84. doi: 10.1080/14740338.2017.1335303

List of Conference Abstracts

1. Artime E, Qizilbash N, Rubino A. A qualitative and quantitative review of additional risk minimistaion measures for EU centrally authorised products, 2006-2014. Drug Saf. 2015;38:935–1048.
2. Artime E, Qizilbash N, Rubino A. Additional Risk Minimisation Measures to Prevent Medications Errors in the EU. Pharmacoepidemiol Drug Saf. 2016;25(Suppl. 3):3–680.
3. Vora P, Artime E, Soriano-Gabarro M, Qizilbash N, Asiimwe A. Review of Cross-sectional Survey Studies evaluating Risk Minimisation Measures in European Union (EU) using the EU electronic Register of Post-Authorisation Studies. Pharmacoepidemiology & Drug Safety 2017; 26(Suppl. 2): 3-636. doi: 10.1002/pds.4070
4. Vora P, Artime E, Soriano-Gabarro M, Qizilbash N, Asiimwe A. A review of studies utilising secondary data to evaluate the effectiveness of Risk Minimisation Measures in European Union (EU) using the EU electronic Register of Post-Authorisation Studies (EU PAS Register). Pharmacoepidemiology & Drug Safety 2017; 26(Suppl. 2): 3-636. doi: 10.1002/pds.4070
5. Artime E, Vora P, Asiimwe A, Soriano-Gabarro M, Qizilbash N. Qualitative Approaches to Testing Data Collection Instruments in Survey Studies Evaluating the Effectiveness of Risk Minimisation Measures in the European Union. Pharmacoepidemiology & Drug Safety 2017; 26(Suppl. 2): 3-636. doi: 10.1002/pds.4070
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the European Union. Pharmacoepidemiology & Drug Safety 2017; 26(Suppl. 2): 3-636. doi: 10.1002/pds.4070

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11. Artime E, Shui I, Tcherny-Lessenot S, D'Arbigny P, Mendez I, Qizilbash N Pre/Post Effectiveness Evaluation of the Myozyme (Alglucosidase Alfa) Safety Information Packet. Pharmacoepidemiol & Drug Safety 2018;27(Suppl. 2):3–521. doi: 10.1002/pds.4629
12. Artime E, Shui I, Tcherny-Lessenot S, D'Arbigny P, Mendez I, Qizilbash N. Pre/post survey to assess the effectiveness of updated Risk Minimisation Materials for an orphan disease: Wave 1 results. DIA 2018
13. Artime E, Vora P, Asiimwe A, Soriano-Gabarro M, Qizilbash N. Quantitative Analysis of Survey Studies Assessing the Effectiveness of Risk Minimisation Measures: State of The Art. Pharmacoepidemiol & Drug Safety 2018;27(Suppl. 2):3–521. doi: 10.1002/pds.4629
14. Artime E, Qizilbash N. Risk minimisation studies outcomes and process indicators. Pharmacoepidemiol & Drug Safety 2019;28(Suppl. 2):5-586. doi: 10.1002/pds.4864

Participation in Relevant Projects / Initiatives

1. Participation in the design and implementation of other six EU RM studies (not currently published).
2. Systematic Review and meta-analysis of PASS Studies Assessing the Effectiveness of Risk Minimisation Measures, available at: http://www.encepp.eu/encepp/viewResource.htm?id=23435
3. Member of the Special Interest Group (SIG) in Benefit Risk Assessment, Communication and Evaluation (BRACE): https://community.pharmacoepi.org/communities/community-home?communitykey=a4c3eb22-64b9-4db9-a781-3a4ba63768f8&tab=groupdetails
4. Former Member of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) SIG on Measuring impact of pharmacovigilance activities

As a member of the SIG, participation in the development of: Annex 2 to the Guide on Methodological Standards in Pharmacoepidemiology 'Guidance on methods for pharmacovigilance impact research'. Available at: http://www.encepp.eu/standards_and_guidances/methodologicalGuideAnnex2.shtml

5. Conduct of research presented at the EMA Workshop on Measuring the Impact of PV Actions (6th Dec 2016): https://www.ema.europa.eu/en/documents/presentation/presentation-measuring-impact-review-survey-studies-evaluate-effectiveness-additional-risk_en.pdf
6. Conduct of research presented at the EMA Information Day Workshop on Measuring the Impact of PV Actions (14th Nov 2017): https://www.ema.europa.eu/en/documents/report/report-workshop-measuring-impact-pharmacovigilance-activities_en.pdf
7. Peer reviewer for relevant journals in the Doctoral Thesis scientific area including *Drug Safety* and *Pharmacoepidemiology & Drug Safety*.

1. Table of Contents

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2. List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AR	Assessment Report
aRMM	Additional risk minimisation measures
ATC	Anatomical and Therapeutic Class
BfArM	Federal Institute for Drugs and Medical Devices
BRACE	Benefit Risk Assessment, Communication and Evaluation
CIOMS	Council for International Organizations of Medical Sciences
CPA/EE	Cyproterone acetate/ethinylestradiol
CPRD	Clinical Practice Research Datalink
DHPC	Direct Healthcare Professional Communication
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EMBASE	Excerpta Medica dataBASE
ENCePP	European Network for Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance
ENT	Otolaryngologist
EPAR	European Public Assessment Report
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
EU-RMP	European Union Risk Management Plan
FDA	Food and Drug Administration
FSR	Final Study Report
GI	Gastrointestinal
GP	General Practitioner
GVP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
ICPE	International Conference on Pharmacoepidemiology & Therapeutic Risk Management
IQR	Interquartile Range
irAR	Infusion-related adverse reactions
ISPE	International Society for Pharmacoepidemiology
IV	Intravenous
MAHs	Marketing Authorisation Holders
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHRA	Medicines and Healthcare products Regulatory Agency
PAC	Patient Alert Card
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PhV	Pharmacovigilance
PMDA	Pharmaceuticals and Medical Devices Agency
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RA	Rheumatoid Arthritis

RIMES	Risk Minimisation Evaluation Studies
RM	Risk minimisation
RMEv	Risk minimisation evaluation
RMM	Risk minimisation measures
rRMM	Routine risk minimisation measures
RMP	Risk Management Plan
SC	Subcutaneous
SD	Standard Deviation
SIG	Special Interest Group
SmPC	Summary of Product Characteristics
SPAF	Stroke Prevention in Atrial Fibrillation
TB	Tuberculosis
VH	Viral Hepatitis

3. Introduction

3.1. Background

Therapeutic risk minimisation (RM) has become an area of extensive research in recent years with the release of specific guidance from the main regulatory agencies worldwide [e.g. Food and Drug Administration (FDA) in 2005 [1], European Medicines Agency (EMA) in 2014 [2], Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in 2012 [3]). Risk minimisation with additional risk minimisation measures (aRMMs) refers to the implementation of strengthened requirements for medicinal products where safety concerns are not sufficiently addressed by routine measures alone [e.g., Summary of Product Characteristics (SmPC), patient leaflet]. Within this context, the evaluation of whether aRMMs work as intended is a key aspect of the product RM strategy. Differences in post-marketing safety regulatory policies are noted across regions [4]. This thesis concentrates on studies that evaluate the effectiveness of aRMMs (hereinafter *EU RM studies*) within the European setting.

3.1.1. Regulatory Context

Regulatory guidance on the development of the EU Risk Management Plan (EU-RMP) was first released in November 2005 [5], becoming a key component of the EU centralized authorisation procedures for medicinal products. In line with regulatory guidance [6], the EU-RMP summarizes the increasing knowledge on the safety profile of an authorised medicine throughout its lifecycle, including any study planned for this purpose (i.e. pharmacovigilance studies), and any measure introduced to minimise the therapeutic risk associated with its use. With these regulatory changes, the EU-RMP became legally enforceable [7]. In the European Union (EU), marketing authorisation holders (MAHs) must submit a RMP to the EMA at the time of application for a marketing authorisation. RMPs are continually modified and updated throughout the lifetime of the medicine.

In December 2010, the European Parliament and European Council adopted the amendments to the EU Pharmacovigilance (PhV) legislation, which came into force in July 2012 with the application of Regulation Nº 1235/2010, Directive 2010/84/EU, and subsequent Commission Implementing Regulation Nº 520/2012 [8–10]. The new PhV legislation introduced significant changes around PhV processes in Europe including the release of 16 guideline modules outlining good PhV practices (GVP) [11,12] and strengthened risk management requirements for medicinal products centrally authorised in EU.

In July 2012, the Pharmacovigilance Risk Assessment Committee (PRAC) was created [13] to help strengthen the safety monitoring of medicines across Europe. The PRAC is responsible for assessing all aspects of risk management of human medicines, including the detection, assessment, minimisation and communication of the safety concerns, design, and evaluation of post-authorisation safety studies (PASS) and PhV audit. The PRAC also provides recommendations on PhV and risk management systems, including the monitoring of their effectiveness [14].

3.1.1.1. Therapeutic Risk Minimisation: Specific Regulatory Guidance in Europe

Risk minimisation measures (RMMs) are "interventions intended to prevent or reduce the occurrence of adverse drug reactions associated with the exposure to a medicine or to reduce their severity or impact on the patient, should adverse reactions occur" [9]. RMMs include routine measures (rRMMs) applied to all authorized medicines (i.e., SmPC, labelling, package leaflet, pack size(s), and legal status of the product) and aRMMs. Most safety concerns are addressed by rRMMs. Additional risk minimisation measures are only introduced when routine measures are deemed to be insufficient for the safe and effective use of a medicine.

In 2009, Aronson et al. proposed a strategy to inform decision-making for regulatory action when new adverse events arise during the lifecycle of a medicinal product, including protective strategies to minimise risks [15]. A regulatory framework for selection, development and evaluation of the effectiveness of aRMMs is available in the Guideline on GVP Module XVI first adopted in 2014 [2] and its addendum [16]. In the same year, the Council for International Organizations of Medical Sciences (CIOMS) Working Group IX published Practical Approaches to Risk Minimisation, which provides a framework for the evaluation of effectiveness of RMMs [17].

Additional risk minimisation measures may differ widely in purpose, design, target audience and complexity. These measures might be used to guide appropriate patient selection with the exclusion of patients where use is contraindicated, to support on-treatment monitoring relevant to important risks and/or management of an adverse reaction. Additionally, specific measures may be developed to minimise the risk of medication errors [18,19] and/or to ensure appropriate administration of the product where it is not feasible to achieve this through the product information and labelling alone.

Table 1 describes the types of aRMMs that may be considered in addition to the routine measures.

Table 1. Types of aRMMs [2]

Type of aRMM	Description
Educational Programmes	
Educational materials for HCPs e.g., brochures or checklists	Contents should provide recommendations on the use, contraindications or warnings related to specific safety concerns described in the RMP referring to the SmPC and the package leaflet for additional information. The material would include guidance on prescribing, including patient selection, testing and monitoring; administration or dispensing procedures; management of risks; how and where to report adverse reaction of special interest.
Educational materials for patients/caregivers e.g., brochures	Contents should aim to enhance patient/caregiver awareness of the early signs and symptoms of specific adverse reactions and actions to take. The material would include guidance on correct administration of the product or remind the patient on any action that needs to be taken e.g., inform HCP.
Patient card	Tool that can be carried with ease to ensure that information regarding the patient's current therapy and its important risks is held by the patient at all times and reaches the relevant HCP when needed. The information should be kept to the minimum necessary.

Type of aRMM	Description
Controlled Access Programmes	
Controlled Access Programme	Programme that established the requirements that need to be fulfilled before the product is prescribed, dispensed or used. These programmes should only be considered in special circumstances where the restriction is required to ensure its safe use. Controlled access programmes may involve testing, examination of the patient, documentation of receipt, procedures for patient follow-up, dispending only by pre-approved pharmacies, etc.
Other measures	
Pregnancy Prevention Programme (PPP)	A PPP aims to minimise pregnancy exposure (i.e., female patients not pregnant when starting therapy or to prevent pregnancy during the course of treatment during treatment) with a medicinal product with known or potential teratogenic effects. A PPP may include educational tools targeting HCPs or patients, controlled access at prescribing or dispensing, counselling, etc. A pregnancy registry may as well be set up to track pregnancy outcomes.
Direct Healthcare Professional Communication (DHPC)	A DHPC is a communication tool targeted at HCPs to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.

Marketing authorization holders are required to monitor the outcome of aRMMs. Evaluation of effectiveness of RMMs is important to manage the benefit-risk balance of a medicinal product. Further details on RM evaluation are provided in Section 3.1.3.2.

Relevant regulatory guidance documents are summarised in Figure 1 and Table 2.

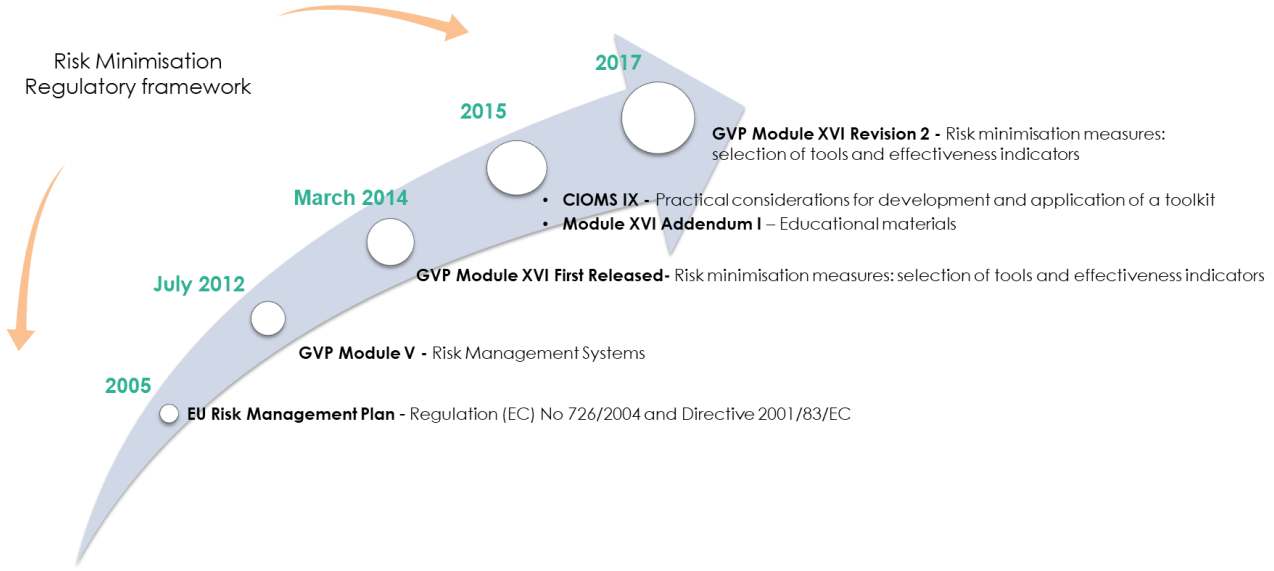


Figure 1. Key Milestones in Regulatory Framework – Risk Management & Risk Minimisation

Table 2. Regulatory guidance on RM in Europe (currently effective)

Regulatory Document / Effective Date	Description
Guidance on the format of the RMP in the EU – in integrated format [20] Effective Date: **Oct 2018**	Provides a template for EU-RMPs
GVP Module XV – Safety communication [21] First released in Jan 2013 Effective Date of 1st Revision: **Oct 2017**	Guidance on how to communicate and coordinate safety information concerning medicinal products authorised in the EU, with particular consideration to DHPCs.
GVP Annex II – Templates: Communication Plan for Direct Healthcare Professional Communication [22] First released in Jan 2013 Effective Date of 1st Revision: **Oct 2017**	Provides a template for DHPCs
GVP Annex II – Templates: Communication Plan for Direct Healthcare Professional Communication (CP DHPC) [23] Effective Date: **Oct 2017**	Provides a template for communication plan of DHPCs
GVP Module VIII – Post-authorisation safety studies [24] First released in Jul 2012 Effective Date of 3rd Revision: **Oct 2017**	Provides general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted voluntarily or pursuant to an obligation imposed by an EU competent authority; describes procedures whereby an EU competent authority may impose on a marketing authorisation holder an obligation to conduct a PASS; describes procedures that apply to non-interventional PASS pursuant to an obligation imposed by an EU competent authority for the protocol oversight and reporting of results, for subsequent changes to the marketing authorisation
GVP Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators [2] First released in Mar 2014 Effective Date of 2nd Revision: **Mar 2017**	Guidance on the principles for the development and implementation of aRMMs, including examples of RM tools. The evaluation of the effectiveness of RMMs.
GVP Module V – Risk management systems [25] First released in Jul 2012 Effective Date of 1st Revision: **Oct 2017**	Guidance on the principles of risk management planning. This Module includes the principles of RM and should be read in conjunction with GVP Module XVI and GVP Module XVI Addendum I on educational materials
GVP Module XVI Addendum I – Educational materials [16] Effective Date: **Dec 2015**	Guidance on the submission of draft education materials to the competent authorities of Member States as well as guidance for these competent authorities on the assessment of such materials, in particular as regards the format and content. Individual Member States may have additional requirements, and as such this guidance should be followed together with other national guidelines
Good practice guide on risk minimisation and prevention of medication errors [19] Effective Date: **Nov 2015**	This good practice guide is one of the key deliverables of the Agency's medication error initiative and offers guidance on RM and prevention of medication errors. The guidance includes population-specific aspects in paediatric and elderly patients, as well as guidance on the systematic assessment and prevention of the risk of medication errors throughout the product life cycle.

Regulatory Document / Effective Date	Description
Risk minimisation strategy for high-strength and fixed-combination insulin products Addendum to the good practice guide on risk minimisation and prevention of medication errors [26] Effective Date: **Nov 2015**	Guidance as a checklist to ensure that the risk of medication errors is addressed consistently for all high strength insulins/fixed combination insulins and in line with the regulatory requirements specified in GVP Module V on risk management planning and GVP Module XVI on RMMs: selection of tools and effectiveness indicators.

3.1.1.2. European Risk Management Plan (EU-RMP)

The EU-RMP is a key requirement for medicinal products centrally approved in Europe. Planning, implementing, or evaluating the effectiveness of aRMMs are key elements of the EU-RMP [20].

The EU-RMP includes:

1) Safety Specification: identification or characterisation of the safety concerns for the medicinal product including the risks that need to be further characterised or managed proactively. Adverse reactions are referred to as safety concerns in the EU-RMP. In the EU-RMP, a list of all safety concerns for the medicinal product is included. A safety concern is any of the important identified risks, important potential risks, or missing information included in the EU-RMP.
2) Pharmacovigilance Plan: routine or additional pharmacovigilance activities (i.e. studies) in place to characterise and quantify serious or clinically relevant risks of adverse reactions, and to identify new adverse reactions. Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification irrespective of whether the studies are to identify and characterise important risks/missing information, or to assess the effectiveness of aRMMs [20]. Studies conducted after authorisation of the medicinal product to further investigate or characterise the safety profile of the drug are known PASS.
3) RM Plan: rRMMs or aRMMs planned or in place including the evaluation of the effectiveness of these activities. In the EU-RMP, a list of all RMMs, additional or routine, is included.

3.1.1.3. Post-Authorisation Safety Studies

A PASS is any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety concern, confirming the safety profile of the medicinal product, or of measuring the effectiveness of RMMs [24]. A PASS may be pursuant to an obligation imposed by a competent authority (categories 1 and 2) or initiated, managed, or financed voluntarily by a MAH (categories 3 and other). A description of the PASS categories is provided in Table 3.

Table 3. Categories of PASS in the EU-RMP [27]

Category	Description	Status
1	Imposed as an obligation	Mandatory and subject to penalties

Category	Description	Status
2	Imposed as a specific obligation in the framework of a marketing authorisation granted under exceptional circumstances	Mandatory and subject to penalties
3	Required in the RMP to investigate a safety concern or to evaluate the effectiveness of RMMs	Legally enforceable
Other	Not obligations or required studies in the RMP but which could provide relevant information on the safety profile of the product	Non-imposed PASS, not required in the RMP

For non-interventional PASS imposed as an obligation, the draft study protocol shall be submitted by the MAH to the PRAC or to the national competent authority of the Member State that requested the study. The final study report (FSR) shall also be submitted to the competent authority within 12 months of the end of data collection. Requirements and recommendations for submission of the protocol and FSR are specified in Module VIII Addendum I [28]. Regulatory Assessment Reports (AR) are generated by the competent authorities in response to the FSR submission, either requiring changes to the report, requesting supplementary information or approving the report with no further changes or discussion. ARs are therefore a source for identifying regulatory consequences, and can be requested to the EMA via the Access to Documents request [29].

3.1.1.4. EU PAS Register

The EU electronic Register of Post-Authorisation Studies (EU PAS Register) is a publicly available source of non-interventional post-authorisation studies (PAS), launched in 2010 and hosted by the European Network for Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance (ENCePP) under the auspices of the EMA [30]. According to the GVP Module VIII, MAHs are legally required to register non-interventional PASS imposed as an obligation (i.e., categories 1 and 2). It is also recommended to register all category 3 (required in the RMP) non-interventional PASS and any other PASS to support transparency and facilitate the exchange of information between different stakeholders. The EU PAS Register includes study documents such as study protocol and report of the registered studies (based on status—planned, ongoing, or completed), which provides a unique opportunity to examine study details. Therefore, the EU PAS Register is a valuable resource for PASS, including those evaluating the effectiveness of RMMs and those mandated by EMA.

3.1.2. Products with aRMMs in Europe

Products with aRMMs account for almost a third of centrally authorised products in Europe [31,32]. Zomerdijk et al. reported that 5% of the active substances authorized before the new legislation (up to 2005) had aRMMs, while aRMMs were identified for 29% of the active substances approved after the new legislation (2006-2009). Additional RMMs were most frequently agreed for active substances concerning 'alimentary tract and metabolism', 'anti-infectives for systemic use' and 'antineoplastic and immunomodulating agents' [32]. Similarly, a posterior review found that 26% of centrally

authorised products were approved with aRMMs in Europe between 2006 and 2015 (yearly frequency ranging from a minimum of 12% in 2008 to a maximum of 41% in 2010; Figure 2) and the antineoplastic/immunomodulating group being the most prevalent (26%) [31]. All aRMMs consisted of educational interventions, mostly targeting physicians/nurses (96%). Patients were targeted in 50% of instances. A high presence of educational materials (86%, educational material (86%); 4%, black-box warnings; 4%, withdrawals) was also reported in the review by Nkeng et al., which had a wider geographical scope (US, Japan, Canada, Australia, Europe) [33].

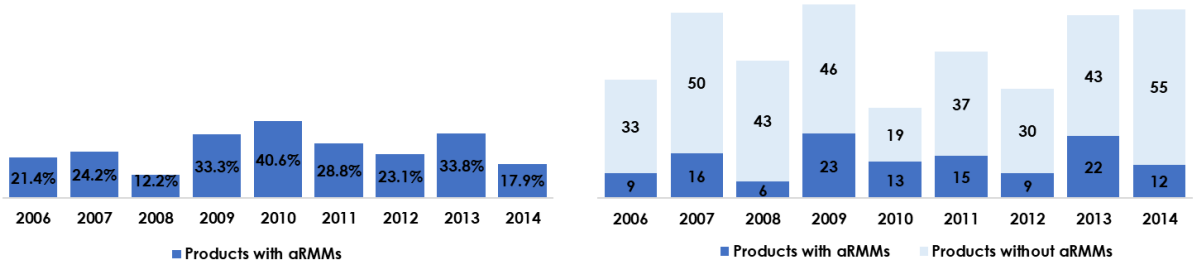


Figure 2. Frequency of aRMMs imposed for centrally approved medicinal products in Europe (Adapted from [31])

A review of RMPs for products assessed by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK showed that 42% of approved RMPs included aRMMs between 2005 and 2011 [34]. The most frequent types of risks requiring aRMMs were adverse drug reactions (39%) and medication errors (23%).

Zomerdijk et al. defined key elements (also referred to as key messages in this report) as components of aRMMs agreed by regulatory authorities at European level [35]. Each aRMM may have multiple elements. The median number of key elements was 9.5 per active substance. As shown in Figure 3, while 36% of the 801 identified key elements aimed to accomplish knowledge changes, 57% referred to behavioural changes. Key elements for HCPs, which mainly addressed behavioural changes (64%), were most frequently classified as "recommended actions regarding drug prescription" and "recommended actions regarding the drug administration process". Of the key elements targeted at patients, 56% addressed behavioural changes, mainly consisting of "recommended actions to be followed during treatment use".

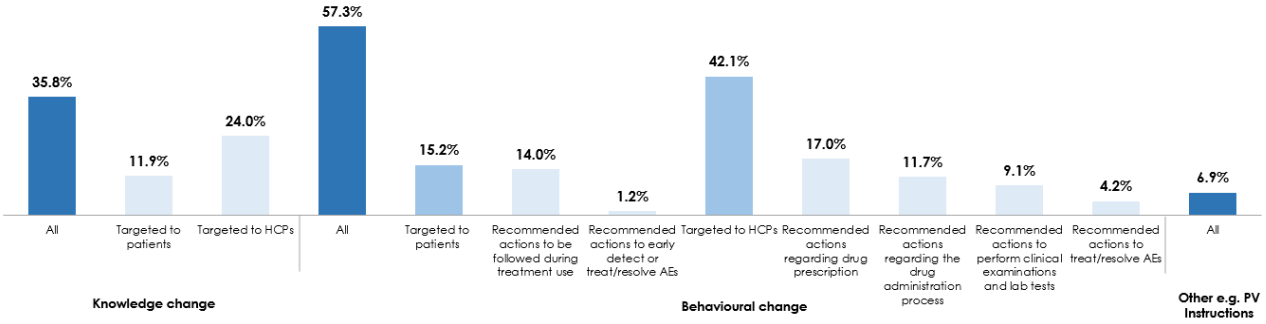


Figure 3. Key elements in identified aRMMs (Adapted from [35])

3.1.3. Risk Minimisation Planning

The introduction of aRMMs should be considered as a "programme" where specific interventions, an implementation plan and evaluation approach are planned and developed. This would start with the selection, development and implementation of the most appropriate measure, and finish with the evaluation of its effectiveness, which may have consequences on the aRMMs.

3.1.3.1. Selection, development, and implementation of aRMMs

aRMMs may be requested by a regulator or proposed by the MAH to minimise a safety concern. When designing the RM Plan, careful consideration should be given to the following aspects:

- Safety concern(s): nature and frequency of the safety concern(s).
- Type(s) of interventions: a RM plan may consist of one or multiple interventions/aRMMs. The types of aRMMs that may be implemented are summarised in Table 1. The specific aRMMs in place for centrally approved products are available via de EMA website (i.e., in the SmPCs and European Public Assessment Reports). The local adaptations may be accessible through the websites of the competent authorities in each country (e.g. RMM Directory of the electronic Medicines Compendium in the UK [36], Centre for the Information of Medicines in Spain [37]).
- Contents and implementation of the materials: The core materials and their key messages are generally agreed centrally with EMA. However, the local adaptation and implementation plan, including the procedures to reach the target population, should be devised and agreed locally with the competent authorities in the countries where the product is or will be launched. What works in a country may not work in the other. The aRMMs implemented with the agreed key messages are available in the SmPC and summary RMP from the EMA website. Local agencies may as well make the final materials in local language available via their websites.
- Timing of implementation: in some instances, safety concerns are identified at time of central authorisation and thus aRMMs should be implemented and made available at that time. In

other circumstances, safety concerns arise with the product already on the market, requiring an action plan after product launch.

- Target audience: this may include HCPs (physicians, nurses, pharmacists) or patients/ caregivers.

Best practices and research methods should be applied in designing and implementing aRMMs to ensure successful RM [38,39].

3.1.3.2. Evaluation of effectiveness of aRMMs

Evaluating the effectiveness of aRMMs is key to establish whether an intervention has been effective or not in reducing product safety concerns, and if not why and which corrective actions are necessary. Prior research in this area reported that the evaluation of effectiveness of RMMs was limited to 31% of medicines which included aRMMs up to 2015, with an accelerated increase detected over time [4].

The effectiveness of aRMMs can be evaluated by process and/or outcome indicators.

- *Process indicators* measure the extent to which aRMMs were implemented (e.g., receipt of the materials by the target audience), whether they are used as expected (e.g., if the target audience reads the materials or whether they distribute them to patients), and the impact of the educational materials on the level of knowledge and/or self-reported behaviour of the recipient around key safety messages.
- *Outcome indicators* provide an overall measure of the level of risk control achieved by the aRMM. Impact on safety outcomes can be assessed, for example, measuring changes in rates of an adverse drug reaction or other safety-related outcomes [2] over time (e.g. before and after the implementation of aRMMs). In some instances, indirect or surrogate measures of the safety outcome may as well be used e.g. reduction in hospitalisations, changes in laboratory values [40]. Therefore, these are conjunctively referred to as **health/safety outcomes** in this document.
- Other indicators are designed to assess the impact on behaviour via drug utilisation studies. The term **behavioural outcome** is used in this document to describe indicators which evaluate outcomes of clinical actions (e.g., prescribing behaviour or monitoring of clinical or laboratory parameters). These have been considered in this document as a separate entity in the evaluation of effectiveness as they constitute intermediate endpoints between processes and final safety outcomes.

Prieto et al. was the first to describe the dual-evidence framework with process indicators and outcomes for RM evaluation, that later constituted the basis of GVP Module XVI [41]. This was further expanded by Banerjee et al. 2013 which placed particular emphasis on the challenges (e.g. appropriate data collection, perceived and real burdens of performing evaluation on clinical

practice, lack of comparators and benchmarking, and uncertainty about the best outcome measures) and interpretation of study results [42].

The term RM Plan is used in the EU-RMP of centrally approved products to describe the selection of RMMs and the studies/measures designed to assess their effectiveness which are required by EMA. However, if a study to assess the effectiveness of aRMMs falls under category 4, it may not be documented in the EU-RMP. Additionally, some products may be nationally approved with studies requested by the national competent authority, in which case national oversight procedures would apply. There may be as well studies independently initiated or conducted by academic groups. Therefore, no existing term has been used prior to this work to designate the combination of studies to assess the effectiveness of aRMMs. The term risk minimisation evaluation (hereinafter '*RMEv*') is newly introduced in this document to describe not only a study, but a group of studies that assess the effectiveness of aRMMs for one specific product. Studies linked to one product are considered part of the product RMEv (Figure 4).

RMEv should ideally include measures of effectiveness at the three levels of evaluation: process indicators, behavioural outcomes and health/safety outcomes. However, this may vary by product.

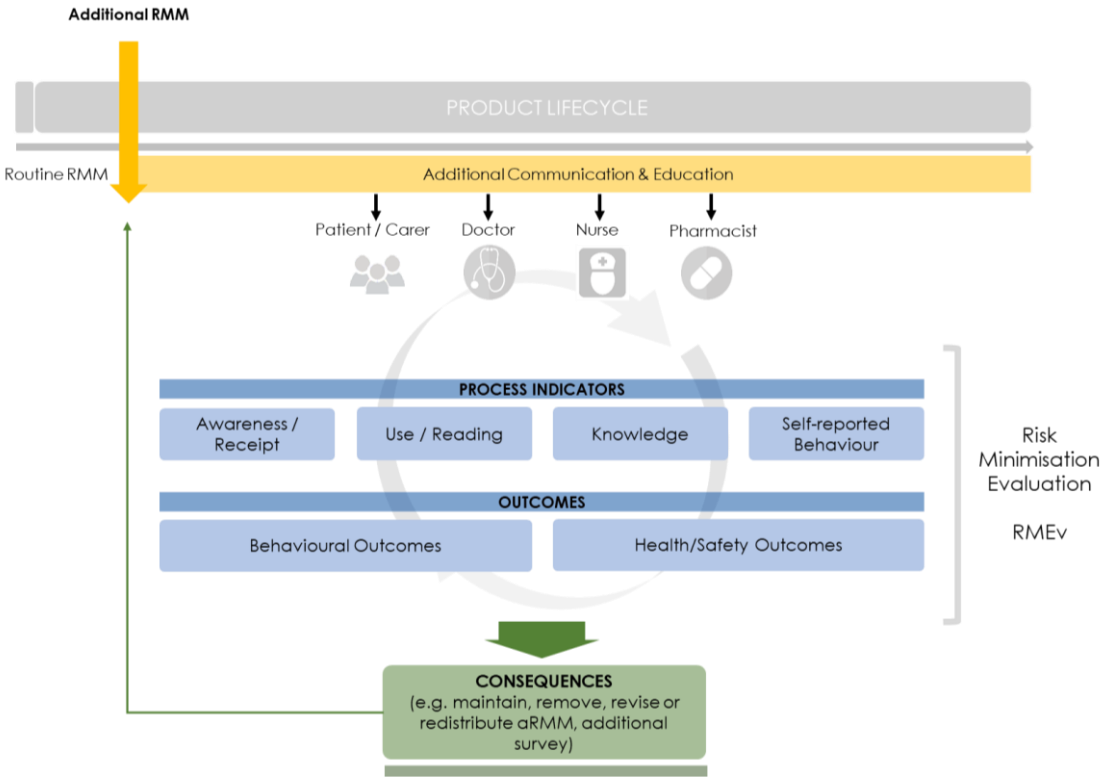


Figure 4. Flow chart of RMEv through process and outcome indicators, during the product lifecycle

When planning a RMEv the following aspects should be considered:

- *Timing of the evaluation:* time points which may be relevant for evaluation include after initial implementation of a RM programme (e.g., within 12-18 months), on one occasion or on

multiple occasions, in time for the evaluation of the renewal of a marketing authorisation, before and after the implementation of aRMMs, etc.

- *Measures of effectiveness:* process indicators and/or outcomes may be measured. MAHs are encouraged to measure both process indicators and outcomes [2], however, this is performed only for certain products. In these cases, in which outcomes are not measured, the effectiveness of the implemented aRMMs may solely be based on the interpretation of results of process indicators.
- *Number of studies and design approach:* while some RMEv consist of one only study, others may be formed by multiple studies which supplement each other. The evaluation approach should consider whether one or multiple evaluations are needed.
- *Geographical scope:* countries where aRMMs have been implemented and where the evaluation of effectiveness proves feasible, representative, and reliable.
- *Study population:* the selection of the study population should be consistent with the study objectives and audience of the aRMMs.
- *Threshold of effectiveness:* certain study designs (e.g., surveys) may benefit from a predefined threshold to guide effectiveness interpretation. However, there is no clear guidance on whether this should or should not be part of evaluation plans.
- *Key contents targeted in the assessment:* evaluations must be proportional and aligned with the intended objective of the key messages in the aRMMs e.g., behavioural changes versus knowledge changes. Refer to section 3.1.2 for further details on the key elements of materials.

3.1.3.2.1. Methodological approaches to inform effectiveness evaluation

Studies with a RM objective use standard epidemiological methods which may involve primary data collection (e.g., surveys or prospective designs) and secondary data use via medical chart abstraction or analysis of existing databases. The ENCePP Guide on Methodological Standards provides general guidance on study approaches and methods, while Annex 2 provides specific guidance and recommendations on methods for measuring the impact of PhV activities [43]. However, creativity is needed to find the most appropriate approach to address the specific needs of the study, which in some instances may require a combination of designs and measures.

Survey studies (hereinafter *EU RM Surveys*) are primarily conducted to assess process indicators. Methods for survey methodology and main requirements for RM evaluation are outlined in GVP Module XVI [2]. The ENCePP Guide on Methodological Standards was recently updated to include, among other changes, a chapter about survey methodology [44].

3.1.3.2.2. Quantification and characterisation of the evaluations

Leading research groups in the field, from regulatory, academic and industry settings, conducted reviews to characterise the type of evaluations available in the literature to assess the effectiveness of aRMMs in Europe (Table 4) [31,35,45–50].

About one third of the products with aRMMs had studies to assess their effectiveness [31,48], and are generally initiated upon request by a regulatory authority [45,51]. Of the 188 aRMMs identified by Gridchyna et al. worldwide between 2000 and 2010, effectiveness was evaluated in 35% [48]. Rubino and Artime reported that effectiveness evaluation was limited to 31% of medicines centrally authorised between 2006 and 2015 in Europe [31].

Process indicators and changes in behaviour were frequently measured in effectiveness studies, while safety outcomes were limited to a minority of cases. The review by Mazzaglia et al. identified 59 studies for cardiovascular, endocrinology, and metabolic indications, most assessing process indicators (n=44), and only 15 assessing safety outcomes [47]. Gridchyna et al. reported that most of the studies (75%) evaluated changes in behaviour through prescribing or laboratory test practices, one quarter evaluated the effect on the occurrence of adverse events [48]. Farcas et al. used the EU PAS register as the main source of EU RM studies, registered up to June 2018 [45]. Of 29 studies with RM objectives identified, all assessed process indicators (mainly knowledge and behaviour), five also assessed outcomes (dual-evidence evaluation approach). By contrast, the review by Goedecke et al., which had a broader scope (studies assessing the impact of regulatory action), found that more than half of the studies measured changes in drug utilization patterns, 27% evaluated health outcomes, and 18% targeted knowledge, behaviour, or changes in clinical practice [50].

Most studies used a survey design, followed by retrospective designs based on medical records or existing databases. In Vora el al., 11/19 included studies were cross-sectional surveys mostly involving HCPs, and 8/19 used secondary data sources (2/8 involved chart review using electronic medical records while 6/8 studies used multiple health care database) [51]. Of 29 studies identified in Farcas et al., 24 used surveys and one direct observation of patients/caregivers by HCPs. Nine studies used a retrospective design (retrospective chart reviews (n=4), prescription databases (n=3), disease registry (n=1) and PET scans interpretations (n=1)) [45]. Of 59 studies included in Mazzaglia et al., 25 used electronic healthcare databases and 18 used questionnaires [47].

The interpretation of results and whether pre-specified outcomes were successfully achieved is a key aspect of effectiveness studies. Effectiveness outcomes were considered successful in half of the studies, while the remaining were inconclusive or not possible to assess [52]. Mazzaglia et al. showed that 24/59 studies were completed; 17 being successful, six inconclusive requiring new evaluations, and one terminated early due to new safety restrictions and evaluation requirements [47]. UK regulatory risk communications were assessed in Weatherburn et al. where significant changes in targeted prescribing and clinical outcomes were observed [53].

Table 4. Summary of published reviews concerning RM

Review Ref.	Period covered	Geographical scope	Review sources	Review scope	Extracted Key Results
[42]	1995 - 2010	European Union	European Public Assessment Reports	aRMMs	aRMMs were identified for 58/391 active substances. The proportion of active substances with aRMMs was 5% among those authorized before, and 29% among those approved after the new risk management legislation. All active substances with aRMMs required the provision of educational material, most frequently involving HCPs (n=57) and the patient (n=31). Thirty-three active substances required aRMMs on top of the provision of educational material, most frequently including patient monitoring and screening (n=19).
[33]	2000 - 2009	Europe, US, Australia	MEDLINE and EMBASE, regulatory agency websites (EMA, FDA, Australian Register of Therapeutic Goods)	aRMMs	A total of 119 aRMMs were identified. Interventions included educational material (31%), black-box warnings (19%) and therapeutic drug monitoring (9%). The website review produced a total of 1112 interventions: 326 posted between the years 2000 and 2004, and 786 between the years 2005 and 2009. The main interventions observed were educational material (86%), black-box warnings (4%) and withdrawals (4%).
[35]	Up to 2011	European Union	European Public Assessment Reports database	aRMMs and the effectiveness of these aRMMs in existing electronic healthcare databases	68 drugs with aRMMs contained 801 key elements of which 57% aimed at behavioural changes. 22% of all key elements, all aimed behavioural changes, were assessed eligible for analysis in existing databases. These mainly concerned recommendations targeted at HCPs regarding drug prescription, e.g., dose recommendations, contraindications or the need to perform laboratory tests for patient monitoring.
[31]	2006 - 2015	European Union	European Public Assessment Reports	aRMMs and the effectiveness of aRMMs	The database encompassed 717 medicines, including 550 non-generic products authorised in 2006–2015. Those authorised with aRMMs accounted for 26%. Yearly frequency ranged from 12% in 2008 to 41% in 2010, though no time-trend was detected. Antineoplastic/immunomodulating products were the most prevalent (26%). All aRMM consisted of educational interventions, mostly targeting physicians/nurses (96%). Patients were targeted in 50% of instances. Effectiveness evaluation was limited to 31% of medicines, though an accelerated increase by year was detected
[54]	2013 - 2017	Europe, the USA, and Japan	Regulatory agencies' websites	New drugs approved with aRMMs	Implementation of aRMMs was 26% (42/159 drugs) in Europe, 8% (15/197 drugs) in the US, and 65% (92/142 drugs) in Japan

Review Ref.	Period covered	Geographical scope	Review sources	Review scope	Extracted Key Results
[49]	1993 - 2017	Worldwide	PubMed, Scopus (including Embase) and Web of Science databases were	Studies of DHPC	A total of 16 studies were included; 12 based on surveys, 2 on document analysis, and 2 primarily on interviews. The prevalent themes included "HCPs have less trust in communication from industry than authorities and medical associations", "HCPs have diverse preferences for how to receive drug risk information" and "Clinical usability of the presented information is less than optimal."
[45]	Up to 2018	Europe	EU Post-Authorization Studies Register	Studies that assessed effectiveness of RMMs	A total of 29 studies were included. Twenty-six studies evaluated aRMMs, employed in case routine interventions are considered insufficient. All studies assessed process indicators, five also assessing outcome indicators, thus using a dual-evidence approach as recommended by the guidelines. However, none of the latter used a pre-post design, comparing the frequency of the adverse outcome before and after the implementation of RMMs. Behaviour and knowledge were the most often assessed process indicators. Outcome indicators included occurrence of adverse reactions, pregnancy, off-label use and medication errors. Only four studies had an established threshold, all for process indicators.
[55]	2012 - 2016	European Union	European Medicines Agency (EMA) website and List of Withdrawn Products, WHO publications (WHO Pharmaceuticals Newsletter and WHO Drug Information) and national regulatory websites and newsletters of all EU Member States	sources of publicly available evidence supporting withdrawal, revocation or suspension of marketing authorisations ('regulatory actions') due to safety reasons	Eighteen single or combined active substances withdrawn, revoked or suspended within the EU for safety reasons between 2012 and 2016 met the inclusion criteria. Case reports were most commonly cited, supporting 94% of regulatory actions, followed by randomised controlled trial, meta- analyses, animal and in vitro, ex vivo or in silico study designs, each cited in 72% of regulatory actions. Epidemiological study designs were least commonly cited (44%). Multiple sources of evidence contributed to 94.4% of regulatory decisions. Death was the most common adverse drug reaction leading to regulatory action (28%), with four of these related to medication error or overdose. Median (IQR) time taken to reach a decision from the start of regulatory review was found to be 204.5 days (143, 535 days) and decreased across the study period. Duration of marketing prior to regulatory action, from the medicinal product's authorisation date, increased
[50]	Up to 2017	Worldwide	MEDLINE and EMBASE	Analytical methods that assess the impact of European Union or non-	A total of 153 articles were included. Over a third of articles studied analgesics and antidepressants. Interventions most frequently evaluated are regulatory safety communications (28.8%), black box warnings (24%) and direct healthcare professional communications (11%); 55% of studies measured changes in drug utilization patterns,

Review Ref.	Period covered	Geographical scope	Review sources	Review scope	Extracted Key Results
				European Union regulatory actions	27% evaluated health outcomes, and 18% targeted knowledge, behaviour or changes in clinical practice. Unintended consequences like switching therapies or spill-over effects were rarely evaluated. Two-thirds used before–after time series and 16% before–after cross-sectional study designs. Various analytical approaches were applied including interrupted time series regression (31%), simple descriptive analysis (29%) and descriptive analysis with significance tests (24%).
[48]	2000 - 2010	Worldwide	MEDLINE and Embase	Methods of evaluation of effectiveness of aRMMs and to identify methodological gaps	A total of 188 aRMMs were identified in the literature, of which effectiveness was evaluated in only 65 (35%) at the time of publication. The largest proportion of studies reviewed (75%) attempted to evaluate changes in behaviour through prescribing or laboratory test practices. One quarter of studies evaluated the effect of aRMMs on the occurrence of adverse events. Only a minority of studies used robust designs, such as randomized controlled trials (9%) or a quasi-experimental design with a parallel comparison group (12%).
[51]	2010 - 2016	European Union	EU PAS Register	Evaluation of effectiveness of RMMs	A total of 19 studies were included. Eleven were cross-sectional surveys and 8 used secondary data sources. Eighty-nine percent evaluated aRMMs (used when routine RMMs are considered insufficient), and 36% evaluated changes in routine RMMs (applicable to all medicinal products). A total of 42 effectiveness indicators were identified: 18 process and 24 outcomes. Half of the indicators were successful; 2% indicators were partially successful; 17% indicators were inconclusive. Effectiveness of the remaining 31% indicators could not be determined owing to limited information. The UK was the most frequent country for the conduct of RM effectiveness studies.
[47]	1995 - 2015	European Union	EMA website, EU PAS Register	Evaluation of effectiveness of aRMMs for Cardiovascular, Endocrinology, and Metabolic Drugs: objectives, design, and the associated regulatory outcomes	A total of 44 studies assessed implementation measures, whereas only 15 assessed safety outcomes. Fifty-one studies used non-experimental designs and 25 studies employed electronic healthcare databases. Of the 24 completed studies, 17 were considered satisfactory and supported immediate regulatory decision making, 6 were considered inconclusive and required new evaluations, and 1 was terminated early because new safety restrictions were required, thereby necessitating a new evaluation.

Review Ref.	Period covered	Geographical scope	Review sources	Review scope	Extracted Key Results
[53]	Up to 2017	United Kingdom	MEDLINE, EMBASE, Scopus and the Cochrane Library	Studies reporting prescribing/health outcome data relevant to UK regulatory risk communication	A total of 40 studies examining 25 UK regulatory risk communications were included. Product withdrawals, restriction in indications and be aware communications were associated with relative mean changes of −78%, −34% and −11% in targeted drug prescribing respectively. DHPCs were associated with relative mean changes of −47% compared to −13% for drug bulletins. Of 7 studies examining unique health outcomes related to the safety concern, risk communications were associated with a mean −10% decrease in intended and a 7% increase in unintended health outcomes. UK regulatory risk communications were associated with significant changes in targeted prescribing and potential changes in clinical outcomes.
[56]	Available on 5 August 2011	European Union	SmPCs	Regulatory rationale and criteria to require a PPP in the EU and to describe the different elements included in the existing PPPs	Five of the seven drugs obtained a PPP based on an established or expected high teratogenic risk in humans. Similarities in the PPPs were: pregnancy tests both before and monthly during drug use; contraceptive use and pregnancy prevention counselling. Differences regarded educational materials, restricted drug supply, continuation of contraceptive use and pregnancy tests after treatment. The last two differences could be explained by pharmacological characteristics of the drug.
[57]	January 1998 to December 2017, updated on January 12, 2019	Worldwide	MEDLINE and EMBASE Federal Institute for Drugs and Medical Devices (BfArM), the EMA, and the FDA websites	Impact of safety warnings on drug therapy	72 studies were identified. A total of 39% studies described the impact of safety warnings on drug therapy as being effective, whereas 17% studies did not. Further, 36% studies described a partial implementation of the warnings (one part of the warning had an impact on drug therapy and another did not). Unintended effects were investigated in 8% studies. While 47% studies examined safety warnings on psychotropic drugs using an interrupted time series design (53%), a before/after (26%), and a time series design (21%), 38 (53%) studied other substances using an ITS design (34%), a before/ after (40%), and a time series design (26%). The proportion of an effective impact on drug therapy was lower in the "psychotropic drugs" group (23%) than in the "others" group (53%).

3.1.3.2.3. Regulatory Evaluation and Consequences

The outcome of the evaluation may be that aRMMs should remain unchanged or modifications are to be made to existing activities (Figure 5). Alternatively, the assessment could as well indicate that the existing aRMMs are insufficient and should be strengthened (e.g., through amendment of warnings or recommendations in the SmPC or package leaflet, improving the clarity of the RM advice and/or by adding additional tools or improving existing tools). Another decision may be that the RMM is disproportionate or lacking a clear focus and could be reduced or simplified (e.g., by decreasing the number of tools or frequency of intervention, or by eliminating interventions proved to be non-contributory to RM) or that the implementation approach is inappropriate and does not reach the target audience. A recent review found a probability of discontinuation of aRMMs of 0.9% within 5 years and 8.3% within 10 years after authorisation, arguing that a lack of robust data on effectiveness of aRMMs may be a potential reason for the low probability of discontinuation [58].

In all circumstances, the burden on the patient and the healthcare system should be given careful consideration [2], minimising the potential for unintended consequences. In fact, Weatherburn et al. provides evidence that unintended consequences may occur when well-intended RM interventions are launched, which supports the need for continuous and systemic evaluation of effectiveness [53].

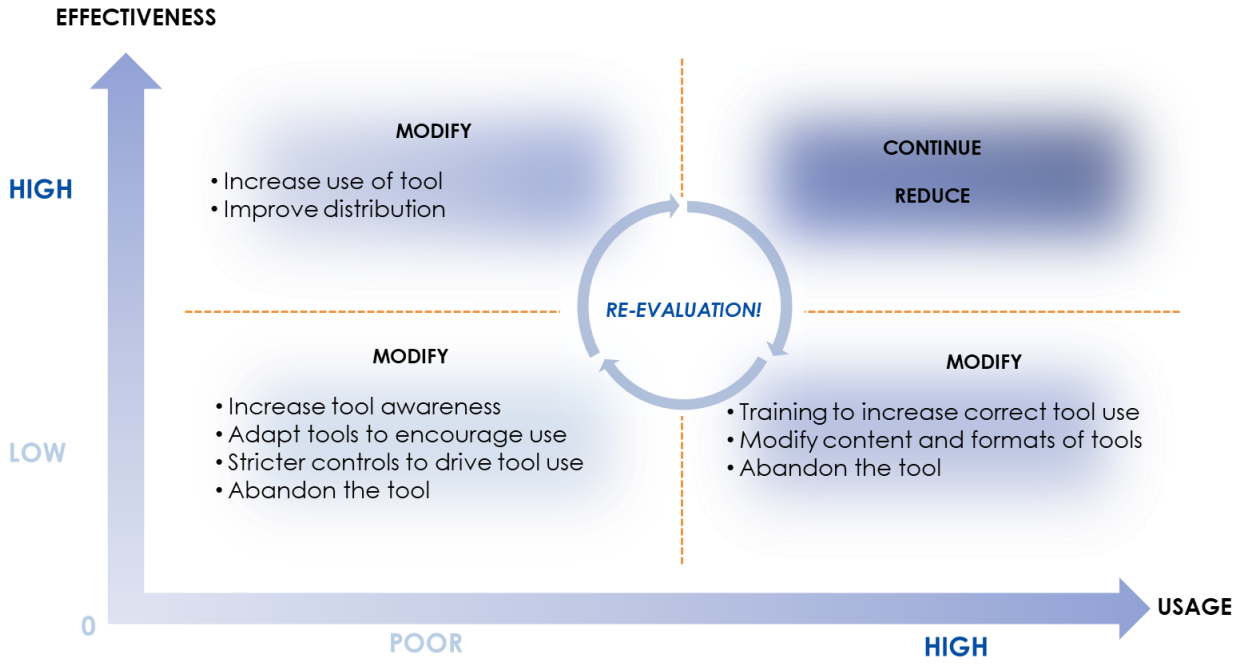


Figure 5. Theoretical framework: consequences of RMEv

3.2. Rationale for this Thesis

Substantial research has been conducted in this field in recent years, since the implementation of the new PhV legislation and the launch of GVP Module XVI. However, certain evidence gaps/needs still remain, which deserve special attention:

- **Need for a quantitative assessment and interpretation of process indicator results across EU RM Surveys**

The registration of PASS in the EU PAS Register has increased steadily over time since its conception. Between 2012 and 2015, half of the protocols submitted to the PRAC for assessment had been entered in the EU PAS Register, 25.4% of which assessed the effectiveness of RMMs [59]. Up to the moment, as shown in our prior review the availability of information on studies of this kind in the public domain (e.g. European Public Assessment Reports) was limited and inconsistent, spread across various product information sources, hindering quantification and characterisation [31]. The publication of protocols and FSRs through the register has provided research groups in the field and MAHs the opportunity to learn from prior experience, and for an in-depth evaluation and interpretation of studies.

While being involved in several studies evaluating the effectiveness of aRMMs and, in particular in those with a survey design assessing process indictors, it became apparent that there was a need for more exhaustive guidance and recommendations to facilitate the practical implementation of these studies, and ultimately allow for standardisation and improved reporting. The International Society for Pharmacoepidemiology (ISPE) Whitepaper on practical challenges and recommendations in RM Survey Studies in Europe developed by members of the Benefit Risk Assessment, Communication, and Evaluation (BRACE) Special Interest Group (SIG) also highlights the need for reflecting on the experience and learn from previous studies [60].

Another prior review we conducted described study characteristics and results qualitatively, underscoring some of the challenges encountered in the interpretation of survey studies e.g. participation, selection and recall bias, study participation [52]. However, there was still a need for a more in-depth evaluation of survey studies by pooling results and providing a quantitative assessment. No previous published review had meta-analysed the results of EU RM Surveys. **Objective 1** of this thesis addresses this research question using the EU PAS Register as the main source of information.

Additionally, regulatory consequences of EU RM Surveys are scarcely described in the literature. A recent review found a low probability of discontinuation of aRMMs after their implementation, however, the reasons for a measure to remain or be removed are not yet fully understood [58]. Therefore, **Objective 1** also aims to further investigate regulatory action as a result of the conduct of the studies.

- **Need to characterise and quantify participation and country selection in EU RM Surveys and the potential for selection bias**

EU RM Surveys rely on the willingness of patients and/or HCPs to participate. As highlighted by our prior work, one main challenge of RM Surveys is participant recruitment which, if not well planned, may limit generalisability and result in selection bias [52]. For example, if those who participate differ from those

who do not, this may result in a non-representative sample. Also, if the pre-specified sample size is not achieved this may affect the robustness of study results. These are also challenges we have encountered when conducting studies of this kind, where the implementation of mitigation approaches such as extension of recruitment periods, reduction of pre-specified sample sizes or the use of research panels was warranted to increase participant recruitment. Some other studies also described operational challenges such as access, approval, feasibility, and resources, which hindered participation. In particular, for patient surveys identifying and contacting patients to participate is particularly difficult due to the inability to directly recruit patients, which usually depends on prescribing physicians, with the potential for resulting in a more biased sample [60].

GVP XVI raises the importance of applying a scientifically sound methodology in EU RM Surveys to promote unbiased and statistically stable results however it also acknowledges a potential selection bias if the selected population is not representative of the target users (i.e. more motivated or educated HCPs and/or patients are more likely to be engaged) [2]. GVP XVI and the ISPE Whitepaper offer some approaches that may help minimize this bias [2,60]: 1) selection of an optimal sample frame considering the characteristics of the population that was targeted for the aRMM such as age, gender, geography, 2) ensuring diversity of the sample frame to allow for sub-group analyses by main characteristics, 3) devise a recruitment strategy with special consideration to the selected survey participant source (e.g. sponsor lists, research panels, societies) and 4) collect the proportion of non-responders and their characteristics to assess the representativeness of the participants. However, the feasibility of deploying these strategies in practice may be limited.

Country selection is another well-known challenge of EU RM Surveys. An ideal sampling frame would include all countries where the aRMMs were implemented, with invitations sent proportionally to the type and number of HCPs per country that were exposed to the aRMMs, and actual survey completion similarly representative. However, feasibility constraints usually limit the sampling frame to a number of countries [60]. Our prior work provides a qualitative overview of participation in EU RM Surveys, with the following key findings for the 11 surveys reviewed [52]:

- All surveys were voluntary, and mainly conducted online.
- The sources of participants varied across surveys: three surveys used a network or an established panel of HCPs, four targeted prescribers/potential prescribers who were sent the RMMs, one selected patients and caregivers who received the aRMMs and the remaining three randomly selected prescribers or potential prescribers of which one also randomly-selected patients.
- The number of included countries ranged from 5 to 10 per survey. The countries most frequently selected were the United Kingdom, Spain, Denmark, Germany, France, Netherlands, and Sweden.

- The total number of participants in the nine surveys was based on pre-specified sample size estimations and ranged from 250 to 802, and the range of participants per country was 2 to 212.

Our previous work additionally suggests that some survey studies had disproportionate participation across countries, which may be a reflection of the usage of the product or difficulties identifying prescribers in these countries. However, the number of surveys in this review was limited. Therefore, there was a need to further characterise country selection and subject participation in EU RM Surveys, investigating the extent to which participating countries contribute participants to the overall sample size. **Objective 2** of this thesis addresses this research question.

- **Need to standardise reporting and enhance quality of EU RM Surveys**

The Risk Minimization Evaluation Studies "RIMES" checklist was recently developed by BRACE SIG members as a first effort to improve the quality of studies evaluating the effectiveness of risk minimization measures [61]. This checklist was applied to a selection of studies identified in a recent review where key opportunities for improvement in reporting were highlighted, including the selection, design, testing and implementation of RMMs, process and outcome metrics, including the extent to which programs reached the intended audience, were integrated into the target healthcare settings, or were sustained over time, and the burden of the program on the healthcare system and implications for patient access [62].

GVP XVI Appendix 1 for the evaluation of the effectiveness of RMMs in survey studies includes testing of data collection instruments, and participation and recruitment strategies [2]. However, this guidance is general and can be widely interpreted. In our prior research we have investigated reporting practices in FSRs of: 1) sampling strategies, 2) recruitment rates, 3) participation data, and 4) qualitative approaches to testing data collection instruments.

1) The sampling frames were mainly lists of HCPs targeted to receive the educational materials (7/13) and panels (4/13). Others used a master list in each country and a list provided by the sponsor. Of the 13 studies, eight used random sampling which was also stratified in two of the studies. However, there was insufficient detail in reports to assess how well the planned sampling method performed and hence assess representativeness of the final results [63].
2) Recruitment rates were reported in less than half of the included studies and the definitions of the numerator and denominator used varied: 3 reported eligible / screened, 3 used reached / invited or contacted / approached, and 2 used completers / eligible. Other rates included: contact rate (contacted / targeted), and cooperation rate (completers / agreed). Response rate was defined as agreed/contacted in one report and screened / (invited-undelivered) in another report. This great variability in reporting participation rates raises the need for standardised reporting and criteria for inclusion in reports [64].

3) Over half of the studies described how participation data had been derived using flowcharts or tables. Participation sets were named and reported differently across studies: 10/13 reported The number of participants invited, 7/13 contacted, 6/13 screened, 7/13 eligible, 5/13 agree, and all reported completers. This shows great variability in reporting participation information [64].
4) A minority of survey studies reported using qualitative methods (no testing was reported for the two patient surveys) with wide variability in terminology [65].

All these highlight the need for additional guidance and standardization of terminology. This is addressed in the **discussion** of this thesis with the provision of recommendations.

- **Need for RMEv approaches that evaluate process indicators as well as outcomes to allow for a comprehensive interpretation of the impact of aRMMs**

RMEv may include studies that evaluate process indicators or outcomes separately, while other RMEv may use hybrid approaches to assess process indicators and outcomes within the same study. Marketing authorisation holders are encouraged to measure both process indicators and outcomes [3]; however, this is performed only for certain products. Prior reviews looked at studies individually, while RMEv as a whole are not well described in the literature. **Objective 3** of this thesis addresses this research question.

- **Linking process indicators and outcomes within the same patients**

More studies with evaluation approaches that assess process indicators and outcomes are warranted, using novel methodological designs. One such example is presented here to address **Objective 4** of this thesis.

Abatacept (ORENCIA®) is a selective immunosuppressant indicated for the treatment of rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis and psoriatic arthritis. As part of a regulatory commitment to the EMA, patient alert cards (PACs) were developed for each formulation (intravenous [IV] and subcutaneous [SC]), to help inform patients and HCPs of the potential risks and actions required during treatment with the product, specifically for infections and allergic reactions. The only difference between the two PACs, both provided in each medicine pack, is that the IV PAC includes a field to indicate the date of the most recent injection, while the SC PAC does not. The principal aim of the PACs is to ensure appropriate action by patients and HCPs when an infection occurs, with the ultimate goal of reducing the occurrence of undesirable outcomes (e.g., hospitalisations), or severity (e.g., reducing delays in seeking medical care). HCPs are expected to be active key players to provide and explain the contents of the PAC to RA patients.

A study to evaluate the effectiveness of the abatacept PACs in RA patients and HCPs using process indicators was conducted. The study design also linked these process indicators with clinical and safety endpoints in the same patients via a chart review sub-study.

4. Objectives

The objectives of this thesis are to:

- **Objective 1:** Conduct a systematic review and meta-analysis of completed survey studies evaluating the effectiveness of aRMMs via process indicators in Europe (hereinafter *EU RM Surveys*):
    a. To describe and summarize EU RM Surveys
    b. To pool data on country selection and participation rates
    c. To pool data on process indicators: receipt, use, knowledge, and self-reported behaviour
    d. To qualitatively assess reporting practices around EU RM Surveys (lessons learned) and provide recommendations
    e. To describe and summarise the submission process and decisions taken by regulators according to regulatory assessment reports[1].
- **Objective 2:** Evaluate participation in EU RM Surveys to assess the effectiveness of aRMMs in Europe:
    a. To describe country selection and participation in EU RM Surveys in Europe
    b. To describe subject participation in EU RM Surveys in Europe
- **Objective 3:** Conduct a systematic review of RMEv that include process indicators and outcomes:
    a. To describe RMEv including process indicators and outcomes to assess the effectiveness of aRMMs with the aim to characterise:
        i. Process indicators
        ii. Outcome measures (behavioural outcomes via drug utilisation studies or health/safety outcomes)
        iii. Evaluation approach (process indicators and outcomes in the same study or in more than one study) and study design (cross-sectional; prospective cohort; retrospective cohort)
        iv. Data sources (surveys, medical chart reviews, prospective data collection, etc.)
    b. To describe general study results and, specifically, the impact of RMEv on process indicators and safety outcomes
- **Objective 4:** Conduct a study to evaluate the effectiveness of aRMMs linking process indicators and outcomes.

[1] Assessment Reports (ARs) are regulatory documents issued by competent authorities which describe the actions/decisions taken by regulators based on the results of the studies

a. To evaluate the effectiveness of abatacept PACs for RA patients and HCPs using process indicators: receipt and use of the PACs, knowledge and implementation of behaviours around key messages in the PACs.
b. To link and correlate process indicators with clinical and safety endpoints in the same patients as a measure of the impact of the PACs.

All these objectives will help draw lessons and recommend guidance on improvements in the methodology and execution of RM studies.

5. Methods

5.1. Objective 1: Systematic review and meta-analysis of completed EU RM Surveys

5.1.1. Search strategy

A literature search was conducted using the EU PAS Register, PubMed and grey literature (i.e., Google) to identify completed EU RM Survey Studies from 1 January 2011 (when the first records appeared in the EU PAS Register) to 31 January 2018. The following terms were used: drug safety, patient survey, health-care professional survey, educational materials, patient alert card, pregnancy prevention, restricted access, dear or direct healthcare professional communication, dear doctor letter, DHPC, risk minimization, additional risk minimisation measures, and aRMMs.

5.1.2. Inclusion criteria

Studies with a cross-sectional survey component assessing the effectiveness of routine or additional RMMs including at least one European country were eligible. Only completed studies with results in the form of FSRs or manuscripts between 1 January 2011 and 31 January 2018 were included.

5.1.3. Data sources

The EU PAS Register, Medline, and Google were used to obtain FSRs and manuscripts of eligible studies. Assessment Reports of the FSRs were sought from the EMA and other national regulatory authorities as they describe the actions/decisions taken by regulators based on the results of the studies. MAHs, the EMA and other national regulatory authorities were contacted to obtain FSRs for completed studies with partial or no results available on the searched data sources. Regulatory documents were requested from EMS via the Access to Documents request form [29]. To compare included versus excluded studies for potential bias, characteristics of the studies were obtained from the protocol in the EU PAS Register where detailed results were not available in the FSRs.

5.1.4. Data extraction

Data were extracted by one reviewer (Esther Artime) and checked by the second reviewer (Pareen Vora), with disagreements resolved by consensus and involvement of a third reviewer (Nawab Qizilbash), if necessary. Data for study characteristics were extracted which include study design (one-wave survey, multi-wave survey, pre- and post-cross-sectional survey, other), target population (general practitioners, specialists, nurses, pharmacists, patients/caregivers), target number of countries included, whether imposed by the regulator or voluntary, Anatomical and Therapeutic Class (ATC) group of the drug, characteristics of the RMMs (routine only, HCP brochures/leaflets/guides, DHPC, patient brochures/leaflets/guides, patient card), number of targeted safety concerns in the RMMs and dates of implementation of the RMMs.

5.1.4.1. Participation data

Independently of the reported proportions, data were also extracted to calculate participation rates based on the number of subjects invited to participate (responders and non-responders), eligible, targeted and completers of the survey, where available. Participation data were abstracted or calculated in two ways: the number of completers divided by number invited [13] and the number of completers divided by number eligible [14].

5.1.4.2. Results of process indicators

Process indicators evaluated in the selected studies (i.e., receipt, reading and use of the materials, knowledge, and implementation of behaviour around key messages) were described. Data on receipt of the materials were extracted for those who participated in the study (i.e., completers) while reading and use of the materials were extracted for those who reported receipt. Use was defined as the proportion of participants who reported having used, carried the materials with them (among patients), handed out and/or explained the materials to patients (among HCPs). The knowledge and implementation of the safety and clinical management messages in the materials were extracted for completers and for those who received, read and/or used the materials.

5.1.4.3. Consequences and decisions taken by regulators based on study results

For studies with ARs available at the time of the analysis, the main regulatory concerns mentioned by regulators (low response rates, selection bias or limited receipt of materials) as well as the decisions taken were extracted. The latter included: no further action or further action (improve distribution of aRMMs or re-distribute, changes to the contents/format of existing aRMMs, pending further discussion/data, follow-up assessment requested, removal of aRMMs, changes to the SmPC, aRMMs implemented or re-analysis by reading/non-reading).

5.1.4.4. Qualitative assessment of reporting practices and provision of recommendations

Based on the revision of final study reports and manuscripts of studies identified in this review, a qualitative assessment of reporting practices will be conducted with additional recommendations for improvements provided.

5.1.5. Statistical analysis

All data extracted (participation, process indicators, and consequences) were described using numbers and percentages.

Data for participation and each process indicator (receipt, use, knowledge, behaviour) were meta-analysed and reported using random effects models. Forest plots with and without pooling are presented. Heterogeneity between studies was assessed with the I^2 statistic [15]. To explore sources of heterogeneity and possible differences in summary estimates, we performed pre-defined subgroup analyses according to the type of aRMMs: HCP brochure, leaflet or guide, HCP checklist, DHPC,

patient brochure, leaflet or guide, and patient card. Study characteristics for included and excluded EU RM Survey Studies (study reports not available) were compared using chi-square to assess study selection bias.

Analyses were performed using excel and MedCalc statistical software.

5.2. Objective 2: Evaluate participation in EU RM Surveys to assess the effectiveness of aRMMs in Europe

5.2.1. Search strategy

A literature search was conducted using the EU PAS Register, Medline and grey literature [Google, International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE) abstracts] to identify completed EU RM Survey Studies from 1 January 2011 (when the first records appeared in the EU PAS Register) to 12 October 2019.

The following terms were used: drug safety, patient survey, healthcare professional survey, educational materials, patient alert card, pregnancy prevention, restricted access, dear or direct healthcare professional communication, dear doctor letter, DHPC, risk minimisation, risk minimization, additional risk minimisation measures, and aRMMs. In the EU PAS Register, all study titles were screened, with search terms used to guide the selection. Where there was uncertainty, study details and documents in the EU PAS Register were reviewed.

Literature reviews identified in the searches were also screened for potential citations.

5.2.2. Inclusion criteria

Studies with a cross-sectional survey component assessing the effectiveness of routine or additional RMMs via process indicators including at least one European country were eligible. Only completed studies with results available in the form of FSR, manuscript or abstract between 1 January 2011 and 12 October 2019 were included.

5.2.3. Data sources

The EU PAS Register, Medline, and grey literature [Google, ICPE abstracts] were used to obtain FSRs, abstracts and manuscripts of eligible studies.

5.2.4. Extraction of participation data

Data were extracted by one reviewer (Macarena Garrido-Estepa) and checked by the second reviewer (Esther Artime), with disagreements resolved by consensus and involvement of a third reviewer (Nawab Qizilbash), if necessary. Data for study characteristics were extracted: 1) target number of countries; 2) number of countries with participants; 3) target population (HCPs, patients/caregivers); 4) target number of participants; 5) invited participants; 6) contacted participants; 7) screened participants; and 8) completers (participant HCPs/patients that completed the survey).

Independently of the reported proportions, participation data were abstracted or calculated as the number of completers divided by number invited. Eligible, targeted and completers of the survey were identified, where available.

5.2.5. Statistical analysis

All participation data were described using number and percentages.

The following were calculated: number and percentage of studies in which each country participated was calculated, number and percentage of completers that each country provided, by study and overall: 1) as the percentage by country of completers provided to the overall number of completers in all studies identified; or 2) as the percentage by country of completers provided to the overall number of completers in studies with that country participation identified.

Response rate was calculated as the percentage of participants who completed the survey among those invited to participate. The range of response rates was described for the total of studies developed in each country.

All analyses were performed using Excel.

5.3. Objective 3: Systematic review of RMEv that include process indicators and outcomes

5.3.1. Search strategy

A literature search was conducted using the EU PAS Register, PubMed, and grey literature [Google, ICPE abstracts] to identify studies of products approved in Europe that evaluated the effectiveness of aRMMs, from 1 January 2011 (when the first records appeared in the EU PAS Register) to 12 October 2019. Systematic literature reviews identified in the searches were also screened for potential citations.

The following search terms were used: drug safety, patient survey, health care professional survey, prescriber education, patient alert card, pregnancy prevention, medication guide, restricted access, dear or direct health care professional letter, dear doctor letter, risk minimisation, risk minimization, drug utilisation, educational materials, DHPC, additional risk minimisation measures and aRMMs. In the EU PAS Register, all study titles were screened, with search terms used to guide the selection. Where there was uncertainty, study details and documents in the EU PAS Register were reviewed.

5.3.2. Inclusion criteria

Identified studies conducted in at least one European country were grouped by product and type of measure (process indicator, behavioural or health/safety outcome). Process indicators were required to have at least one measure of awareness, receipt, use, knowledge, or self-reported behaviour, collected via surveys. Outcome measures included behavioural outcomes obtained via drug utilisation studies or studies measuring monitoring parameters, and health/safety outcomes. Studies linked to one product were considered part of the product RMEv. Only RMEv with both process indicators and outcomes (within one or multiple studies) were included. Additionally, RMEv with study results available in the form of study report, manuscript or abstract were also identified.

5.3.3. Data sources

The EU PAS Register, Medline, and grey literature [Google, ICPE abstracts] were used to obtain FSRs, abstracts and manuscripts of eligible studies. If results were not available at the extraction date (i.e., 12 October 2019), protocols and summaries from the EU PAS Register were used to extract characteristics.

5.3.4. Data extraction

Data were extracted by one reviewer (Esther Artime) and checked by the second reviewer (Macarena Garrido-Estepa), with disagreements resolved by consensus and involvement of a third reviewer (Nawab Qizilbash), if necessary.

Data were extracted at two levels: by product/RMEv, and by study within the RMEv. Product characteristics were extracted which included ATC group, aRMMs (HCP brochures/ leaflets/ guides, DHPC, patient brochures/ leaflets/ guides, patient card), and safety concerns targeted in the aRMMs.

The number of studies linked to each product were computed and RMEv grouped by the number of studies conforming the evaluation (1 study, 2 studies or ≥3 studies).

For studies within each RMEv, the following characteristics were extracted:

1) study design components: survey (patient or HCP survey), retrospective (post-implementation or pre-/post-implementation of aRMMs), prospective, or other study designs;

2) participating countries;

3) type and size of study population (e.g., HCPs, patients, others);

4) measures: a) *Process indicators*: receipt, use, knowledge, self-reported behaviour; b) *Behavioural outcomes*: off-label / on-label / inappropriate prescribing, monitoring, reading errors; c) *Health/safety outcomes*: adverse events and reactions (including those leading to resource use such as hospitalisation, emergency room visits, etc.) and, medication errors, and

5) data sources: healthcare databases, company safety database, medical records data extraction, primary data collection or others.

For RMEv with study results available, the number of participants and/or drug prescriptions, as applicable, were extracted for tabulation. Study results were extracted and presented separately (by RMEv) for process indicators and outcomes. For example, for process indicators, the percentages of participants reporting having received, read or used aRMMs, as well as those reporting correct knowledge and behaviours around key messages were obtained. For outcomes, the reported result of each behavioural (e.g., proportion of off-label use) or health/safety outcome (e.g., number of events) was also extracted and described.

5.3.5. Statistical analysis

Categorical variables are summarised by frequencies and percentages and continuous variables with medians and ranges. Non-parametric statistical methods were used, when appropriate, to assess if the groups had similar statistical distribution (e.g., Mann-Withney U or Kolmogorov-Smirnov test).

Product and study characteristics are presented in tables overall and for RMEv with results available.

All analyses were performed with Stata v.12 and Excel.

5.4. Objective 4: Case Study to Evaluate the effectiveness of aRMMs linking process indicators and outcomes

5.4.1. Study Design

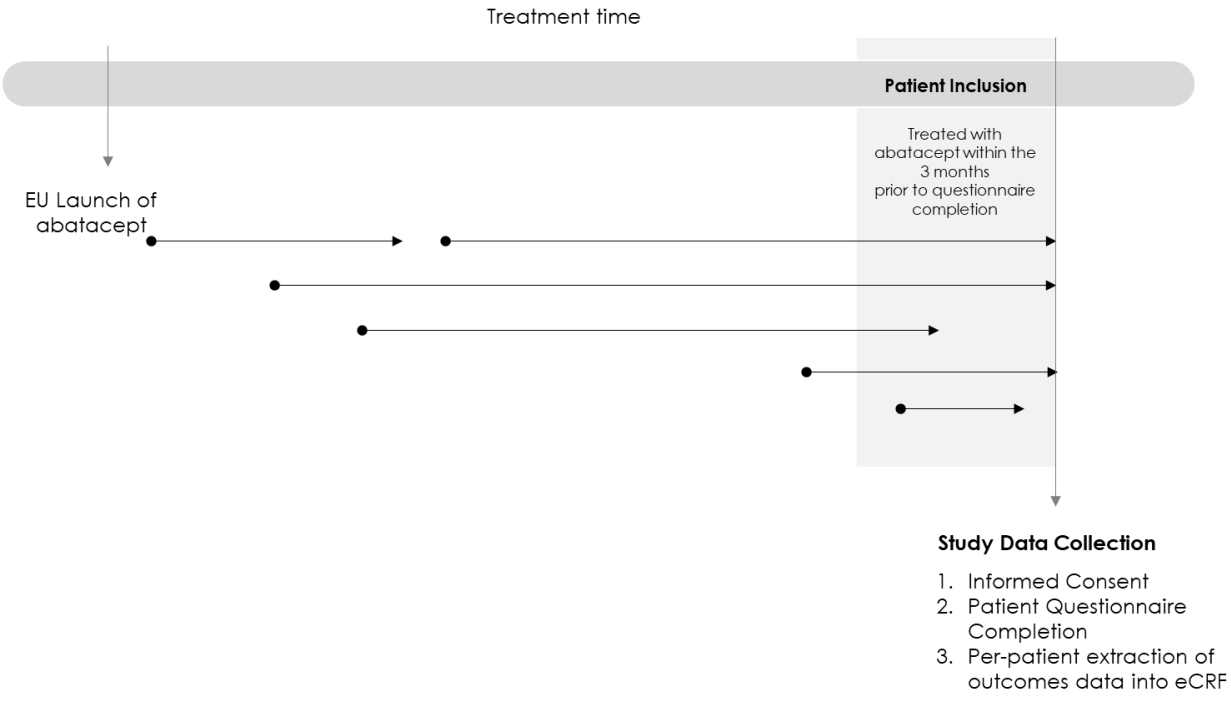
The study consisted of three sub-studies:

- Two cross-sectional surveys for 1) HCPs and 2) patients to assess process indicators (awareness, receipt, utility, utilisation, knowledge, and behaviour related to the PACs) and
- 3) a retrospective chart review of patient data to assess clinical and safety outcomes.

The study was conducted in France, Germany, Spain, Sweden and the United Kingdom.

The details of the study design are illustrated in Figure 6.

Panel A: Patient scenarios valid for inclusion in the study. Horizontal arrows represent abatacept treatment periods for specific patients. Patients who received abatacept within the 3 months prior to the date of questionnaire completion were eligible for participation in the study.



Panel B: Retrospective data collection. Follow-up data were collected for the 2 years prior to the date of informed consent, or less if abatacept was commenced less than 2 years from the date of informed consent.

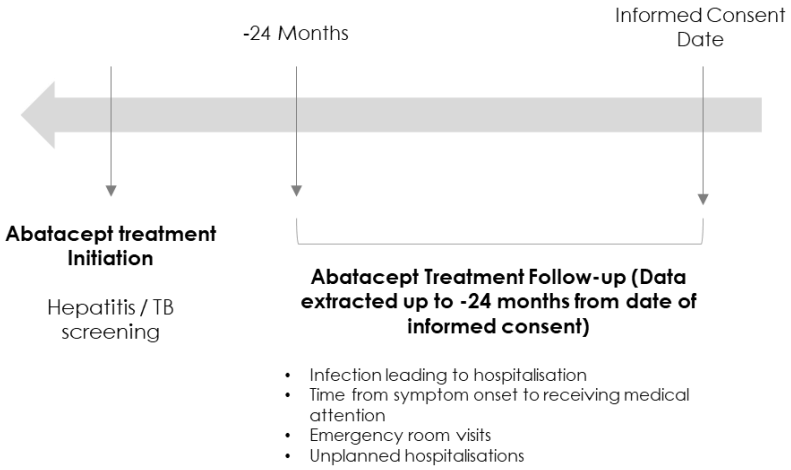


Figure 6. Design features of the three related sub-studies

Panel A shows the scenarios considered valid for inclusion in the patients' sub-studies. In the retrospective chart review sub-study, follow-up data were collected for 2 years before the date of informed consent, or less if abatacept was commenced less than 2 years from the date of informed consent (Figure 6, Panel B).

Key messages contained in the PACs are listed in Table 5.

Table 5. Key Messages in the abatacept Patient Alert Cards

Safety Concerns	Key Messages
Infections	• Patients receiving abatacept are at increased risk of infections • Avoid abatacept in patients with severe infection • Need for screening for infections prior to abatacept: TB and VH • Seek medical attention if symptoms suggestive of infection occur e.g., fever, persistent cough, weight loss, listlessness
Allergic Reactions	Seek medical attention if symptoms of allergic reactions occur including chest tightness, wheezing, severe dizziness and light headedness
Others	• Show the PAC to any doctor who may treat them • Take a full list of medicines on visiting a HCP • Keep the PAC for 3 months after the last dose of abatacept • Document the abatacept start date (IV and SC) • Document the date of the most recent abatacept treatment (IV only) • Complete patient's name and the doctor's name and phone number

The study, classified as a PASS, was conducted according to GVP Modules XVI [2] and VIII [24] and best practices based on guidelines [66–69] and publications [35,41,42,48,50,59–61,70]. The protocol was approved by Ethics Committees in all five participating countries.

5.4.2. Study Population and Sampling

Only patients treated with abatacept for RA in the 3 months preceding the date of completing the questionnaire were included. After informed consent patients received the survey questionnaire. Data were extracted from the clinical medical records of patients who had completed the survey questionnaire.

The following population sets were defined in the patient survey:

- Study Population: All patients in the participating countries identified as potentially eligible to participate in the patient survey.
- Eligible Set: All patients in the who fulfilled the inclusion and exclusion criteria.
- Enrolled Set: All patients in the who participated in the survey.
- Completers: All patients in the who completed the survey and were used in the analysis.

Physicians were selected using random sampling applied to lists of rheumatologists provided by the MAH and panels (Figure 7). Nurses were identified through physicians. Physicians and nurses who recruited patients were not eligible for the HCP survey. ´Fair market´ fees were paid for completed questionnaires.

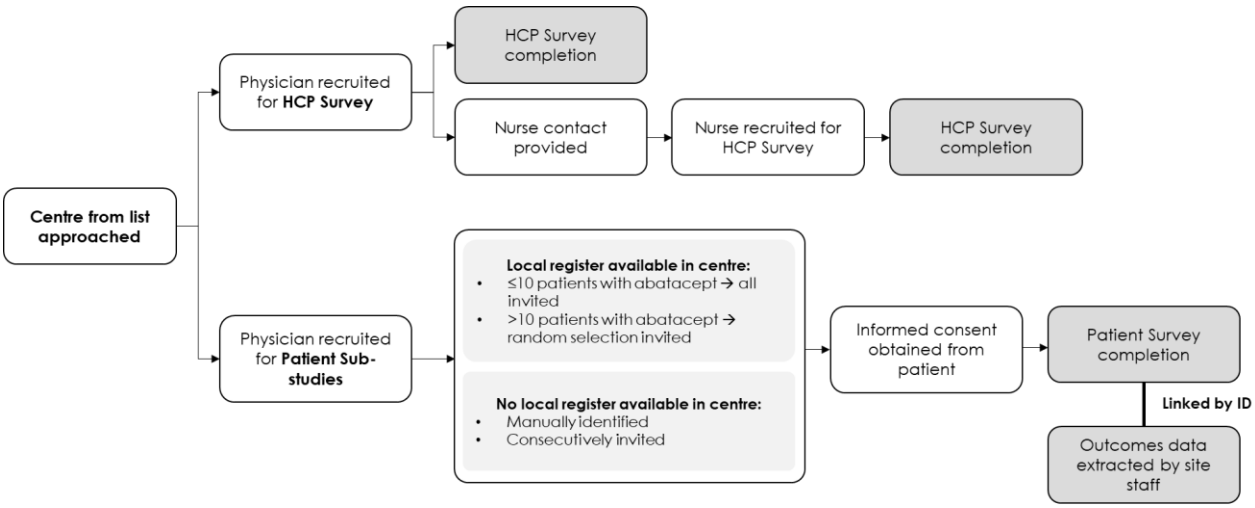


Figure 7. Sampling and recruitment strategy

The following population sets were defined in the HCP survey:

- Invited: All HCPs in the participating countries invited to participate in the HCP survey.
- Evaluable Set: All HCPs in the participating countries who were successfully contacted and agreed to complete the feasibility questionnaire.
- Eligible Set: All HCPs who completed the feasibility questionnaire and fulfilled the inclusion and exclusion criteria.
- Enrolled Set: All HCPs who accessed electronic Case Report Form (eCRF).

- Completers: All HCPs who at least completed the eligibility criteria and socio-demographic questions in the HCP Survey.

Patients and HCPs were identified by a unique code in the Electronic Data Capture (EDC) platform, allowing linkage of patients between the survey and the retrospective chart review.

5.4.3. Data Collection Tools

HCP and patient questionnaires were translated into local languages, and cognitively pretested by HCPs and patients. The questionnaires consisted of multiple-choice questions including conditional branching based on responses to previous questions to improve user friendliness and reduce missing data. Patient questionnaires were completed online or on paper. HCP questionnaires were only available online.

For the retrospective chart review, HCPs or data managers were trained to extract information from patient´s clinical medical records and enter it into the EDC platform. The EDC platform guided data extraction and contained edit checks and management of queries to improve data quality.

5.4.4. Sample Size Calculation

The study aimed to recruit 400 patients to allow precision of less than ±5% around plausible estimates (ranging from 50% to 90%) of correct responses for process indicators related to the PACs. This number would also permit the detection of a moderate decrease in the risk of infection-related hospitalisations (odds ratio <0.23) between patients with ≥80% correct responses versus <80% correct response. A target of 80 HCPs would allow precision ±6.6 to 11.0% around plausible estimates (70% to 90%) of correct responses for HCP process indicators.

5.4.5. Study Endpoints & Data Analysis

5.4.5.1. Healthcare Professional and Patient Surveys

HCPs and patients with questionnaires received before database closure were considered as 'completers'. Participation rates were defined as the number of participants with completed questionnaires among the number invited in each category or among the number eligible [66,67].

The definition of study endpoints and scores is provided in Table 6.

Table 6. Study Endpoints

Study Endpoint	Definition
Awareness	Proportion of HCPs/patients who were aware of the PAC
Receipt	• Proportion of HCPs who had access or received the PAC • Proportion of patients who recalled receiving the PAC
Utilisation	• Proportion of HCPs/patients who recalled having read the PACs • Proportion of HCPs who explained contents to their patients • Overall utilisation score

Study Endpoint	Definition
Utility	• Patient's assessments of understandability and readability of the PACs (clarity, conciseness, completeness, brevity) • Overall utility score In the Patient Survey, the utility score was computed as 100 times the sum score of items assessing clarity, conciseness, completeness and briefness (recoded as 0 = worst value to 4 = best value), and understandability (ranging from 0 to 4), divided by the maximum possible score of 20. In the HCP survey, the utility score was computed as 100 times the sum score of items assessing helpfulness, clarity, conciseness, completeness and briefness (recoded as 0 = worst value to 4 = best value), divided by the maximum possible score of 20. For all other endpoints, the score was calculated as the percentage of correct responses to variables that assessed the endpoint, that is, 100 times the sum of all variables, divided by the number of variables.
Knowledge	• Proportion of HCPs/patients with correct responses to questions related to the important identified risks of infections and allergic reactions associated with abatacept treatment • Overall knowledge score
Self-reported Behaviour	• Proportion of HCPs/patients with correct responses to behavioural questions • Overall behavioural score
Global Score	An average score that summarises the overall correct utilisation of the PAC, correct knowledge, correct behaviour and utility. This score is presented in three categories by tertiles: high level (scores >67%), medium level (scores 34-67%) and low level (scores 0-33%).
Correlation of global score of the patient survey with:	Percentage of patients with: • Results of any test to screen for TB prior to administration of abatacept therapy • Results of any test to screen for VH before administration of abatacept therapy • Infections leading to hospitalization • Infections leading to emergency room visits Average number of days per patient from first symptom onset of infection until receiving medical attention.

Percentages were computed using the number of participants who answered specific questions as the denominator, excluding missing responses. All analyses were performed overall and by receipt versus no receipt of the PAC.

5.4.5.2. Retrospective Chart Review

The extracted outcomes included (Table 6): availability of results of screening tests for tuberculosis (TB) and viral hepatitis (VH) prior to abatacept use (Yes/No), occurrence of infections leading to hospitalisation and/or infections leading to emergency room visits (Yes/No), and time from occurrence of infection to receiving medical attention. Numbers and percentages were calculated for each outcome. The mean number of days between the dates of first symptom onset of the infection and receiving medical attention was calculated.

Univariate analyses correlated within-patient clinical and safety outcomes responses to process indicators in the patient survey. The primary analysis assessed the frequency of infections leading to hospitalisation in patients by tertiles of the patient survey global score of the PAC using a two-sided chi-square test.

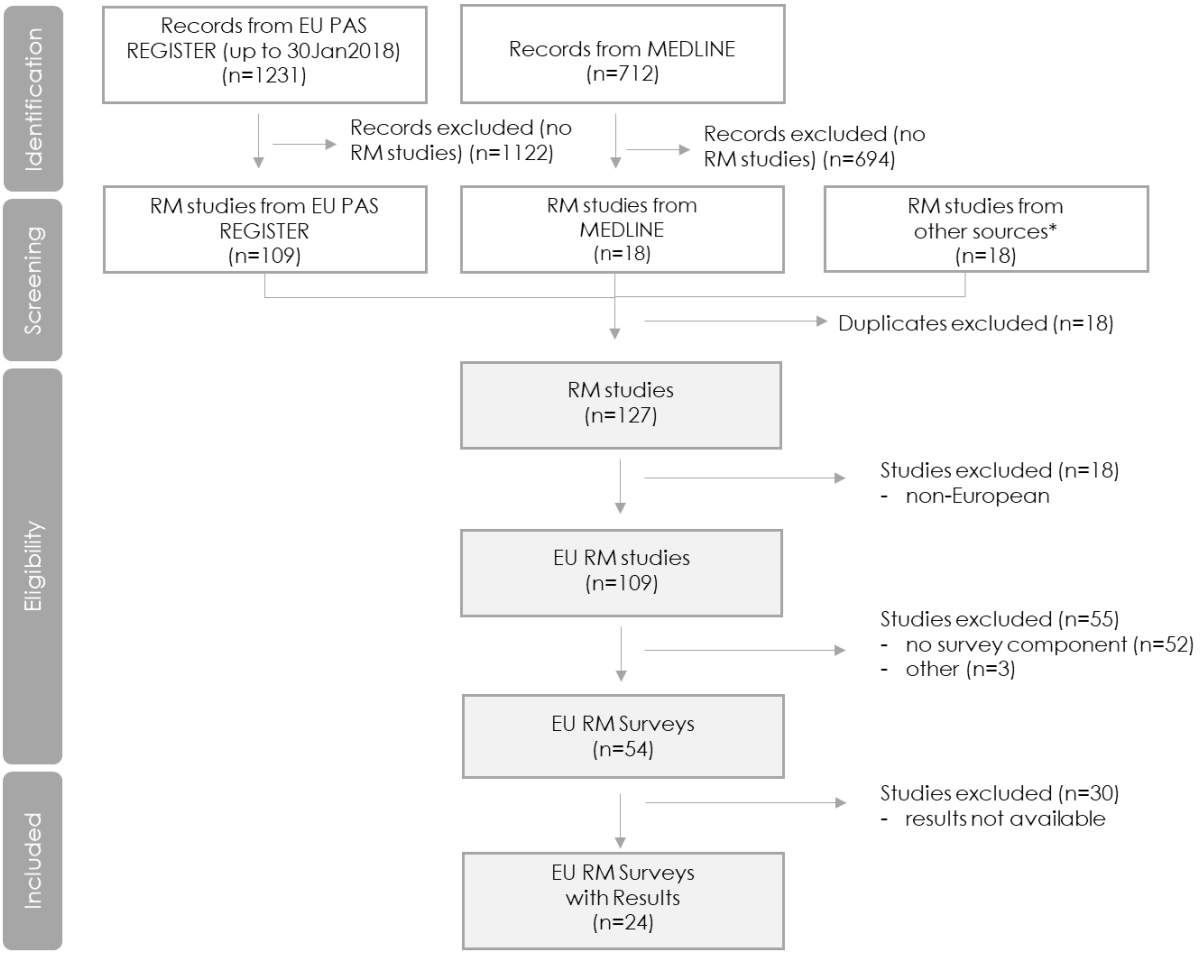
Statistical analyses were performed using SAS Enterprise Guide (versions 9.7) and MedCalc statistical software.

6. Results

6.1. Objective 1: Systematic review and meta-analysis of completed EU RM Surveys

6.1.1. Study Selection

Figure 8 describes the study selection flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. From all studies identified, 127 assessed the effectiveness of RMMs, and a survey component as a method of data collection was identified in 54 studies. A total of 24/54 EU RM Surveys met the inclusion criteria and were analysed using FSRs: 16 from the EU PAS Register, four were obtained from MAHs and four from the EMA. There were 30 studies excluded due to the absence of results, but their study characteristics were available from study protocols or EU PAS Register summaries.



*Internet, selected conferences
Abbreviations: EMA, European Medicines Agency; FSR, final study report; MAH, Marketing Authorisation Holder; NA, National Agency; RM, risk minimisation

Figure 8. Flowchart of the selection process based on PRISMA guidelines – Objective 1

6.1.2. Study Characteristics

The characteristics of the studies included in the analysis are presented in Table 7. Of the 24 studies, 18 (75.0%) were requested by a regulator. Eleven (78.6%) were classified as PASS Category 3. Seventeen (70.8%) were for centrally approved drugs by EMA. Survey designs were one-wave for 21 (87.5%) and multi-wave in 12.5% of studies; no studies had a pre-post survey design. HCPs were included in 23 (96.0%) studies, composed of 91.7% specialists, 58.3% general practitioners (GPs), 20.8% nurses, and 25.0% pharmacists. Patients and/or caregivers were included in 8 (33.3%) studies. There was a mean (SD) of 7 (3) countries targeted per study. Only, two studies evaluated the effectiveness of routine RMMs.

A total of 34 aRMMs were reported in 24 studies: 15 (68.2%) HCP brochures; leaflets or guides; 8 (36.4%) DHPCs; 7 (29.2%) patient cards; and 4 (16.7%) patient brochures, leaflets or guides. Almost half (45.5%) of the studies evaluated materials implemented at the time of drug launch: 7 (31.8%) after a label change, concern for a new safety signal or a restriction of indication; and 4 (18.2%) for an extension of an indication or new formulation. The median (IQR) number of key safety concerns in the materials per study was 3 (1 to 5). The use of pre-defined thresholds to define success was only reported in 7 (29.2%) studies, mostly using 80% or the 'majority of respondents' for the knowledge and/or behaviour endpoints.

Differences between included and excluded EU RM Survey studies without FSRs (Table 7) were identified for types of aRMMs (less patient brochures and more DHPCs were evaluated in the included studies), ATC categories (41.4% of drugs were in the antineoplastic and immunomodulating group in the excluded set versus 16.7% among included studies; 10.3% of drugs belonged to the nervous system category in the excluded set versus 29.9% of included studies), and type of target population (91.7% of included studies involved specialists and 58.3% GPs versus 56.7% of excluded studies involving specialists and 6.7% GPs; $p < 0.01$).

Table 7. Characteristics of Included and Excluded EU RM Surveys

Characteristics	Included EU RM Surveys [N=24]	Excluded EU RM Surveys [N=30]	*P* value
	n (%)	**n (%)**	
Type of RMM			
Routine	2 (8.3)	1 (3.3)	*0.84*
Additional (i.e., aRMM)	22 (91.7)	29 (96.7)	
Patient cards	7 (29.2)	13 (44.8)	
DHPC	8 (36.4)	5 (17.2)	
HCP Brochure/Leaflet/Guide	15 (68.2)	20 (69.0)	
Patient Brochure/Leaflet/Guide	4 (16.7)	20 (69.0)	
Timing of aRMM	**N = 22**	**N = 29**	
At launch	10 (45.5)	17 (58.6)	*0.35*

Characteristics	Included EU RM Surveys [N=24]		Excluded EU RM Surveys [N=30]		*P* value
	n	**(%)**	**n**	**(%)**	
After launch	1	(4.5)	2	(6.9)	
At extension of indication / new formulation	4	(18.2)	1	(3.4)	
After label changes / signal / restriction of indication	7	(31.8)	9	(31.0)	
Drug Approval Procedure					
Central Approval	17	(70.8)	27	(90.0)	*0.15*
National Approval	7	(29.2)	3	(10.0)	
Study Requested by Regulator					
Yes	18	(75.0)	24	(80.0)	*0.91*
No / Unspecified	6	(25.0)	6	(20.0)	
Study Category					
Category 1 or 2 (imposed by regulator)	3	(21.4)	3	(10.7)	
Category 3 (required in EU-RMP)	11	(78.6)	25	(89.3)	*0.99*
Missing	10		2		
Study Design					
One-wave survey	21	(87.5)	25	(83.3)	
Multi-wave survey	3	(12.5)	3	(10.0)	*0.64*
Pre/Post survey	0	-	1	(3.3)	
Other	0	-	1	(3.3)	
Study Population					
Clinical Specialists	22	(91.7)	17	(56.7)	
General Practitioners (GPs)	14	(58.3)	2	(6.7)	
Nurses	5	(20.8)	4	(13.3)	***<0.01***
Pharmacists	6	(25.0)	3	(10.0)	
Patients/Caregivers	8	(33.3)	9	(30.0)	
Physicians unspecified	0	-	7	(23.3)	
No. Target Participating Countries					
1 – 5	9	(37.5)	19	(63.3)	
6 – 10	12	(50.0)	9	(30.0)	*0.17*
>10	3	(12.5)	2	(6.7)	
Mean (SD)	7.1 (3.2)		5.5 (2.7)		
Number of Safety Concerns					
1 – 5	19	(79.2)	19	(67.9)	
6 – 10	3	(12.5)	8	(28.6)	*0.31*
>10	2	(8.3)	1	(3.6)	
Missing	0	-	2		
Median (Q1-Q3)	2.5 (1.0 – 5.0)		3.0 (1.0 – 7.5)		
Pre-specified criteria for success					
Yes	7	(29.2)			
Knowledge and/or behaviour - Majority	3	(42.9)			

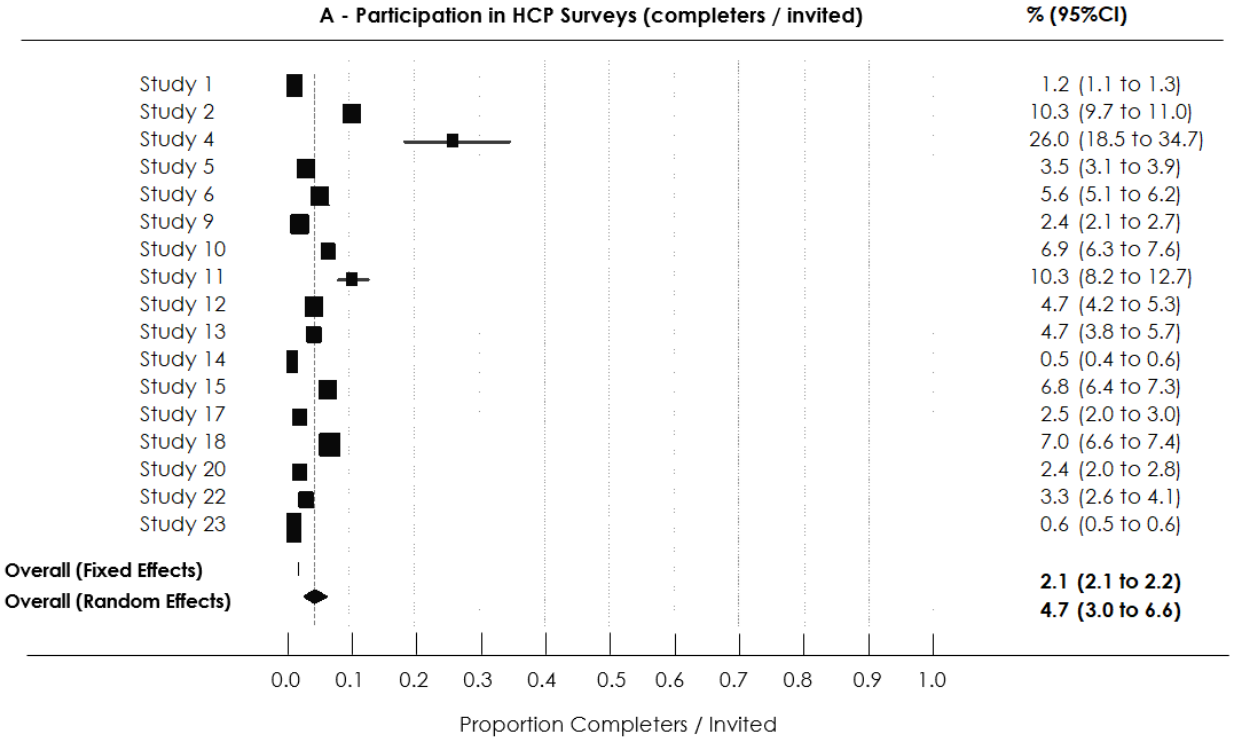
Characteristics	Included EU RM Surveys [N=24]	Excluded EU RM Surveys [N=30]	*P* value
	n (%)	**n (%)**	
Knowledge and/or behaviour - ≥80%	3 (42.9)		
Knowledge - 70%	1 (14.3)		
Receipt - 50%	1 (14.3)		
Use - 35%	1 (14.3)		
Unspecified	17 (70.8)		

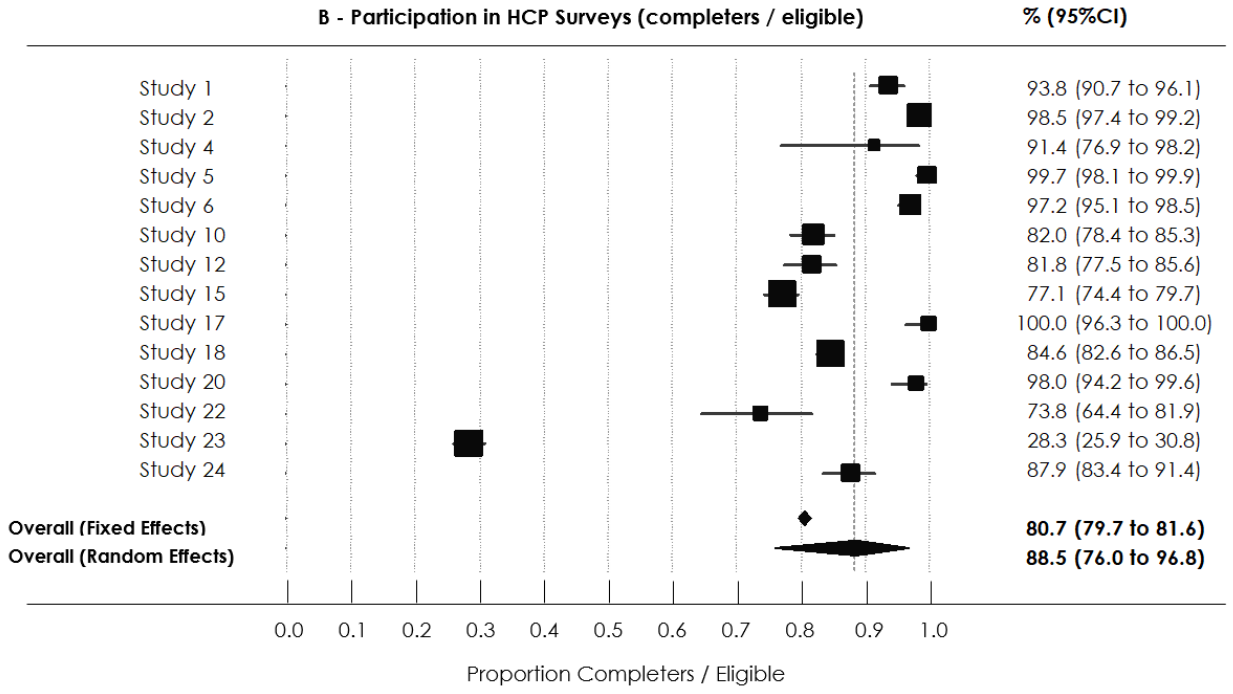
Abbreviations: aRMM, additional risk minimisation measure; GP, General Practitioner; RM, risk minimisation

6.1.3. Healthcare Professional Surveys

HCPs were targeted in 23 of the 24 included studies. The pre-specified target sample size in the study protocol was reached in 52.2% of the 23 studies. Seven of the 11 studied that did not reach the target deviated by more than 10% from the pre-specified size. Fewer studies reached the target sample when only specialists were involved: 37.5% versus 57.1% in studies that also involved GPs ($p = 0.66$).

Participation rates were reported and calculated as a proportion of invited and proportion of eligible (Figure 9 (a,b)). The pooled 'Completers/Eligible' rate was 88.5% ($I^2 = 99.5\%$), while the pooled 'Completers/Invited' rate was 4.7% ($I^2 = 99.7\%$). Despite the great heterogeneity, all studies with data available to calculate 'Completers/Invited' (N = 17) had ≤10% participation, with the exception of one study (Study 4: 26.0%) which was restricted to one country only with a small but targeted number of HCPs invited. Exclusion of this study resulted in a pooled estimate 'Completers/Invited' rate of 4.0%. Studies varied in the outcomes reported: 69.6% of studies reported receipt, 34.8% reading, 47.8% use of materials, 95.3% knowledge/understanding of key safety concerns and 43.5% self-reported behaviour to implement the information.


A - Participation in HCP Surveys (completers / invited)
% (95%CI)
Study 1
Study 2
Study 4
Study 5
Study 6
Study 9
Study 10
Study 11
Study 12
Study 13
Study 14
Study 15
Study 17
Study 18
Study 20
Study 22
Study 23
1.2 (1.1 to 1.3)
10.3 (9.7 to 11.0)
26.0 (18.5 to 34.7)
3.5 (3.1 to 3.9)
5.6 (5.1 to 6.2)
2.4 (2.1 to 2.7)
6.9 (6.3 to 7.6)
10.3 (8.2 to 12.7)
4.7 (4.2 to 5.3)
4.7 (3.8 to 5.7)
0.5 (0.4 to 0.6)
6.8 (6.4 to 7.3)
2.5 (2.0 to 3.0)
7.0 (6.6 to 7.4)
2.4 (2.0 to 2.8)
3.3 (2.6 to 4.1)
0.6 (0.5 to 0.6)
Overall (Fixed Effects)
Overall (Random Effects)
2.1 (2.1 to 2.2)
4.7 (3.0 to 6.6)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion Completers / Invited


B - Participation in HCP Surveys (completers / eligible)
% (95%CI)
Study 1
Study 2
Study 4
Study 5
Study 6
Study 10
Study 12
Study 15
Study 17
Study 18
Study 20
Study 22
Study 23
Study 24
93.8 (90.7 to 96.1)
98.5 (97.4 to 99.2)
91.4 (76.9 to 98.2)
99.7 (98.1 to 99.9)
97.2 (95.1 to 98.5)
82.0 (78.4 to 85.3)
81.8 (77.5 to 85.6)
77.1 (74.4 to 79.7)
100.0 (96.3 to 100.0)
84.6 (82.6 to 86.5)
98.0 (94.2 to 99.6)
73.8 (64.4 to 81.9)
28.3 (25.9 to 30.8)
87.9 (83.4 to 91.4)
Overall (Fixed Effects)
Overall (Random Effects)
80.7 (79.7 to 81.6)
88.5 (76.0 to 96.8)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion Completers / Eligible

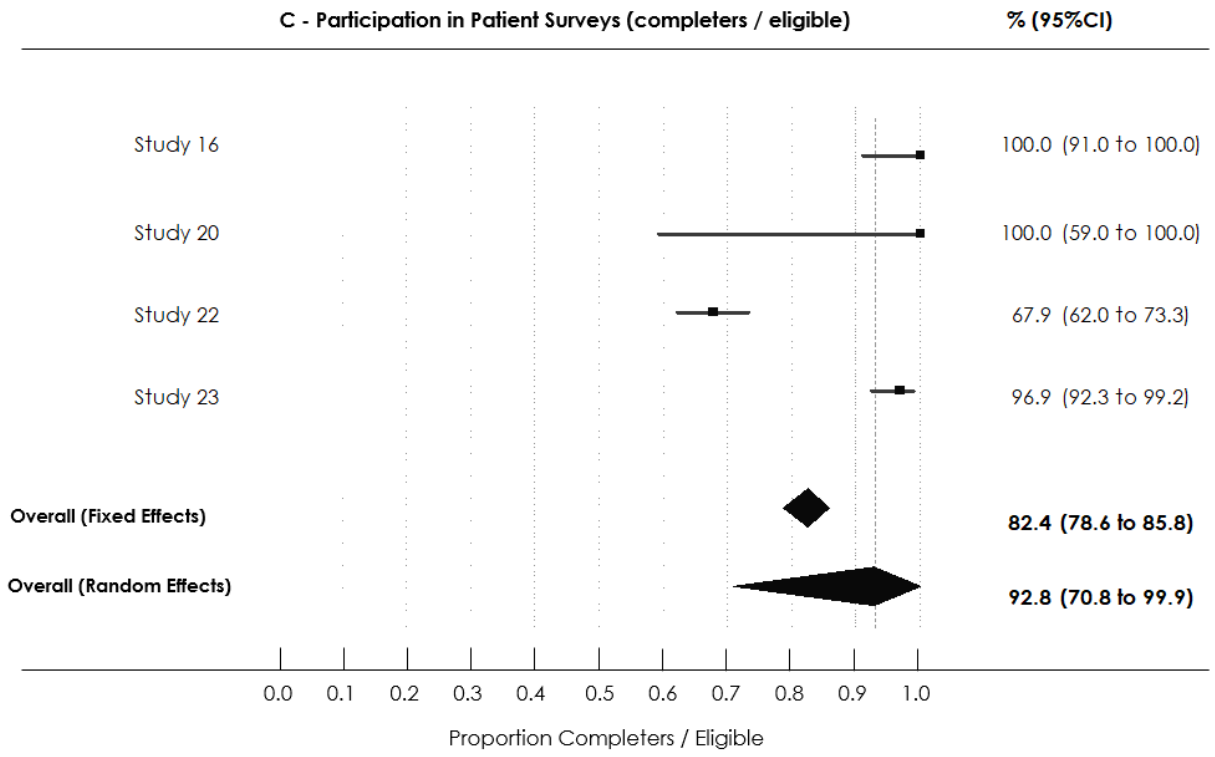
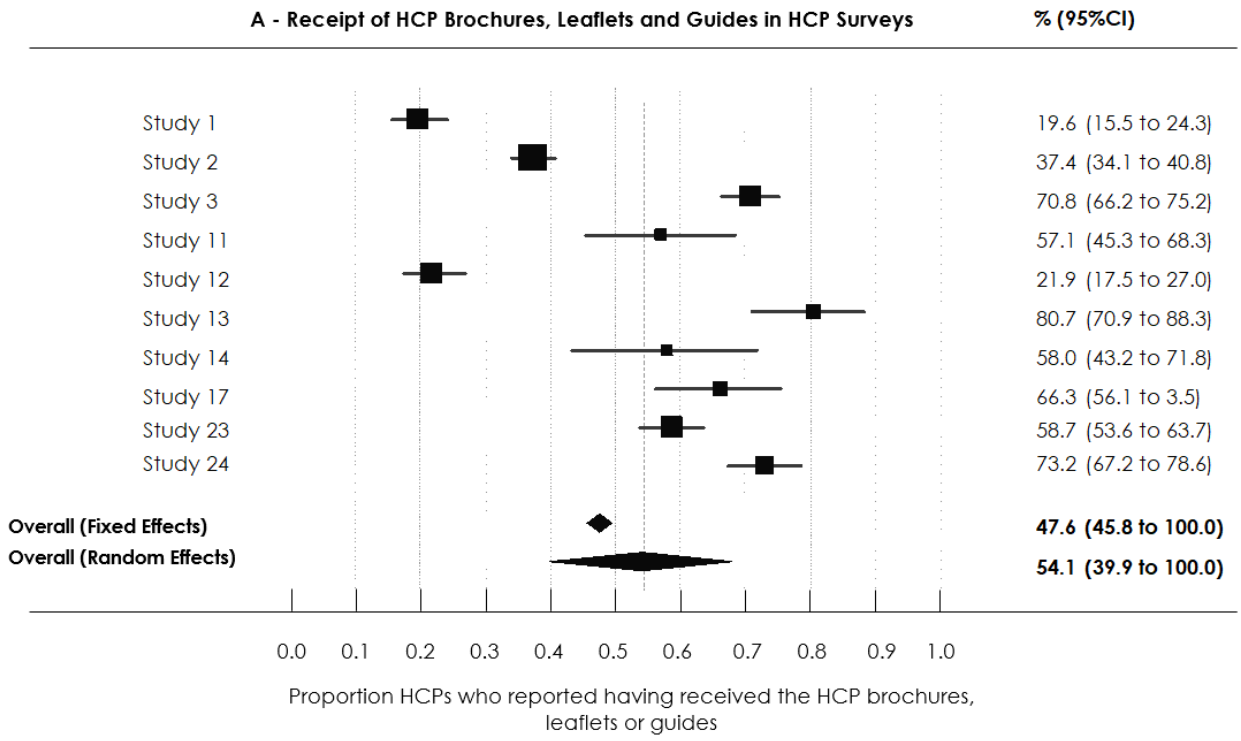
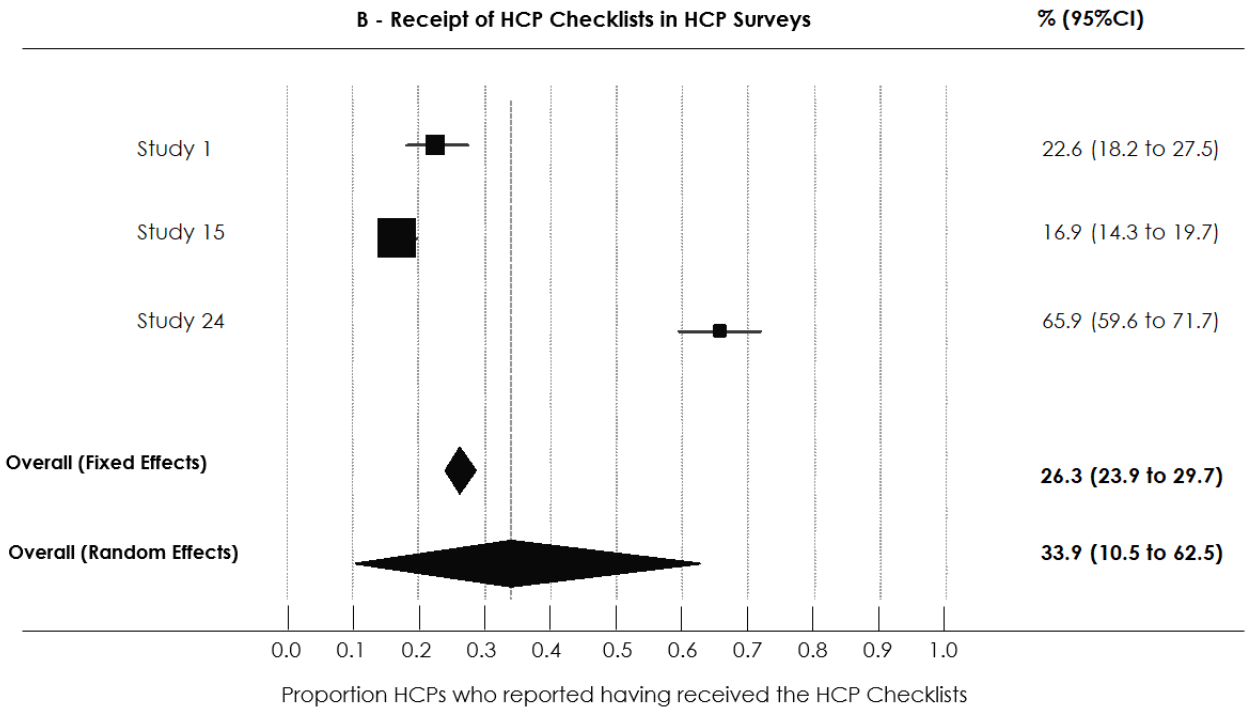


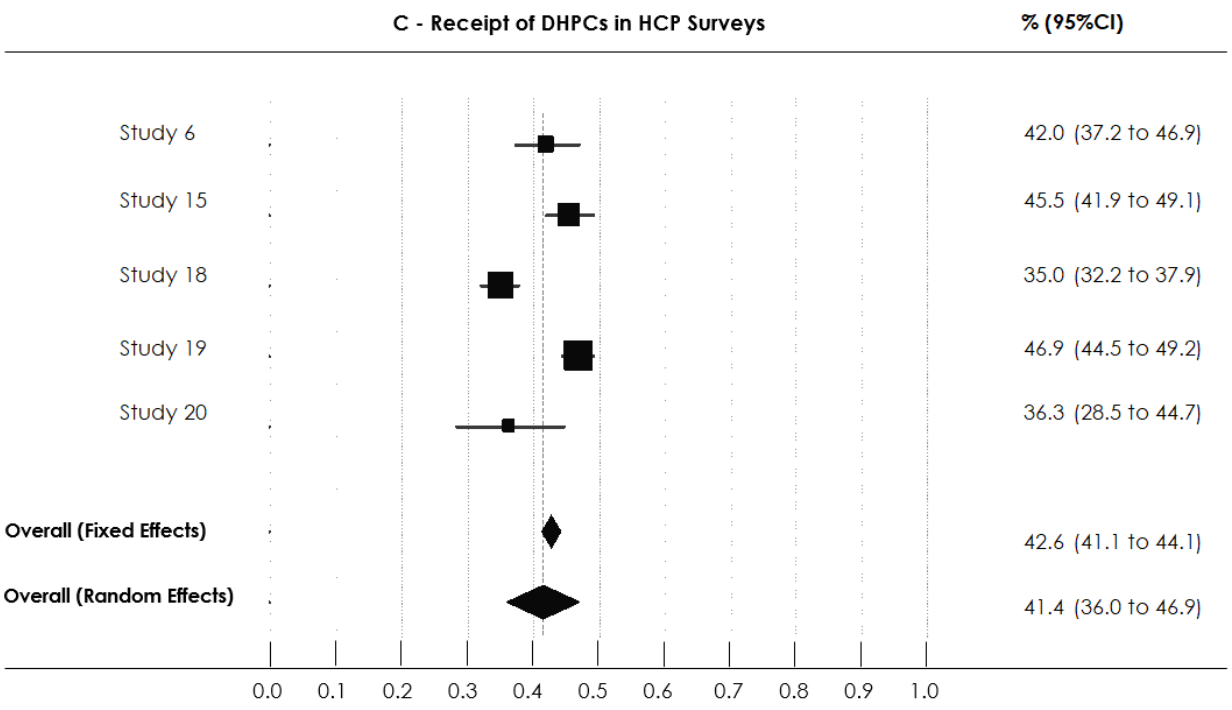
Figure 9. Participation Data in HCP and Patient surveys – Forest Plots

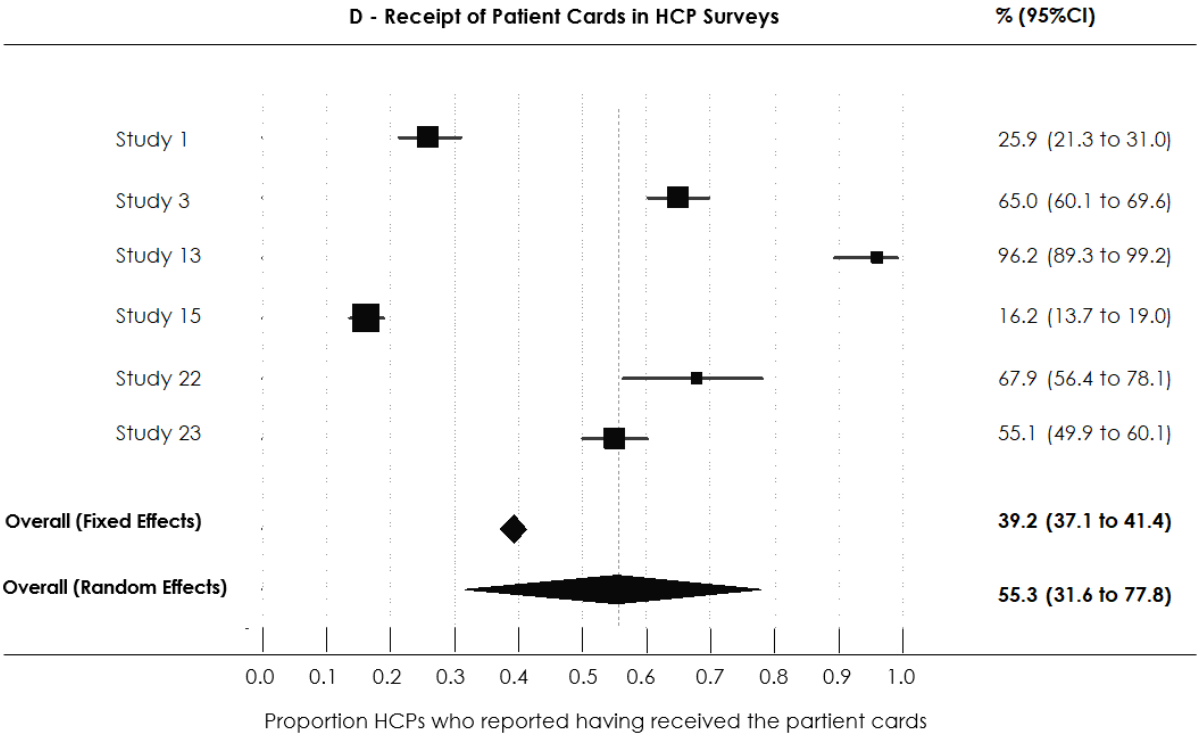
Receipt was reported for 24 materials in 16 HCP Surveys. The proportion who received materials varied widely with no clear trend by type of material. Materials that were distributed together had similar results (e.g., 22.6% reported having received the checklist and 19.6% the brochure in Study 1). Figure 10 (a–d) shows the pooled estimates by type of material based on a few data points that exhibit great heterogeneity: 54.1% (I^2 = 98.2%) for HCP brochures, leaflets and guides; 33.9% (I^2 = 99.0%) for HCP checklists; 41.4% (I^2 = 64.4%) for DHPCs; and 55.3% (I^2 = 99.0%) for patient cards. In eight studies, 89.8% (I2 = 90.0%) of HCPs reported reading all or some of the contents of the aRMMs among those who reported to have received them (Figure 10 (e)). Figure 10 (f–i) show the pooled estimates of use of materials (used, handed out and/or explained to patients) by type of aRMM: HCP brochures, leaflets and guides (71.7%; I^2 = 58.9%), HCP Checklists (72.1%; I^2 = 81.2%), patient brochures, leaflets and guides (87.9%; I^2 = 65.0%), and patient cards (80.4%; I^2 = 85.4%). Knowledge and understanding were reported for 69 safety concerns in 22 studies. The percentage of correct responses was >60% in 76.8% of safety concerns and >80% in 40.6% of safety concerns (Figure 11 (a)). Statistically significant differences in knowledge rates between HCPs who received, used or read the materials and those who did not were found for 7 safety concerns (Figure 11 (c)): squamous cell carcinoma (SCC) ($p < 0.05$; Study 1), urinary retention ($p < 0.001$; Study 5), confusion ($p < 0.001$; Study 5), hallucinations ($p < 0.05$; Study 5), psychosis ($p < 0.05$; Study 5), hypersensitivity to lactose monohydrate ($p < 0.05$; Study 24), and haemolysis and haemolytic anaemia ($p < 0.001$; Study 24). Although non-statistically significant, two

safety concerns ('food intake' and 'anaphylactic/ anaphylactoid reactions') reported lower average knowledge scores in HCPs who did receive, use, or read materials compared with those who did not. Data on the implementation of behaviour resulting from aRMMs could not be abstracted and analysed due to varying ways of reporting.

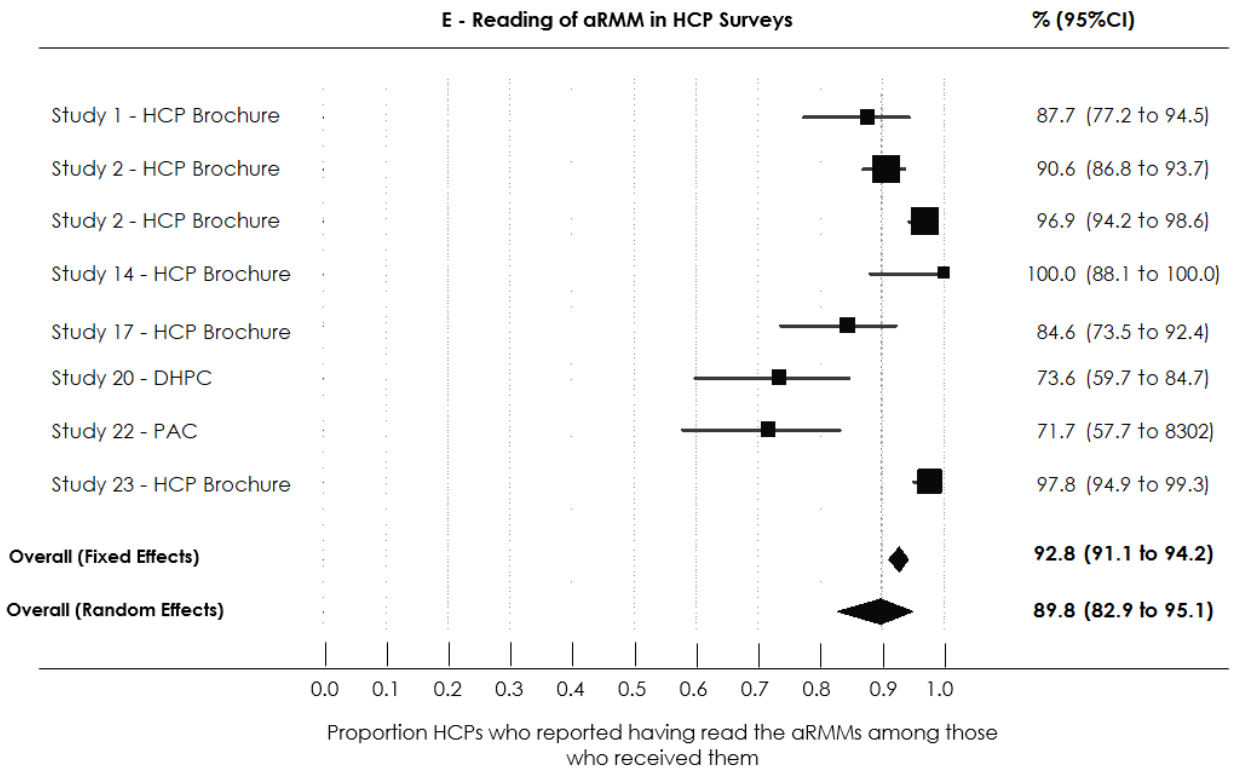


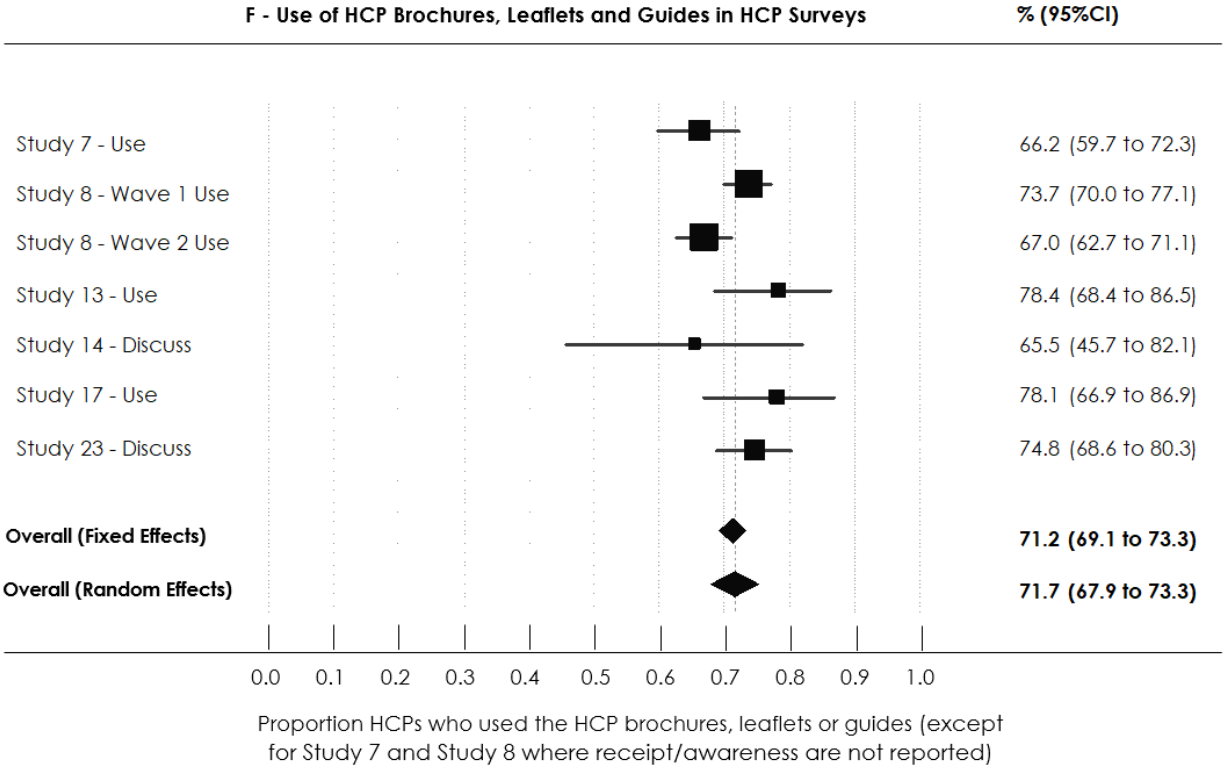


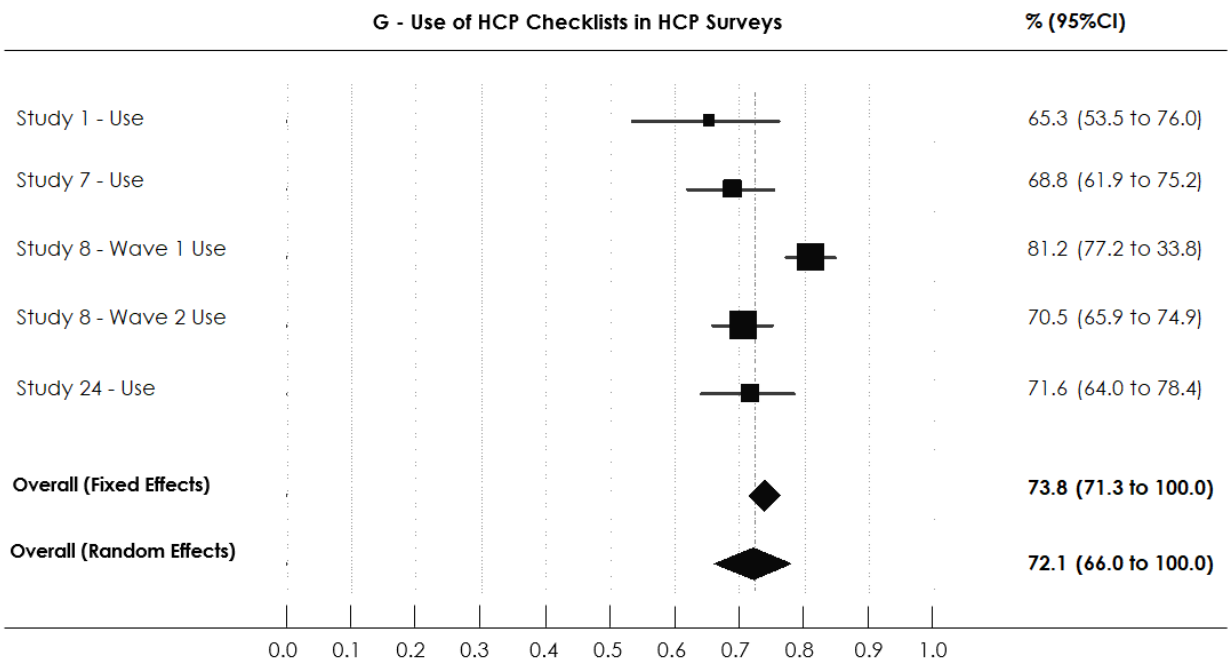


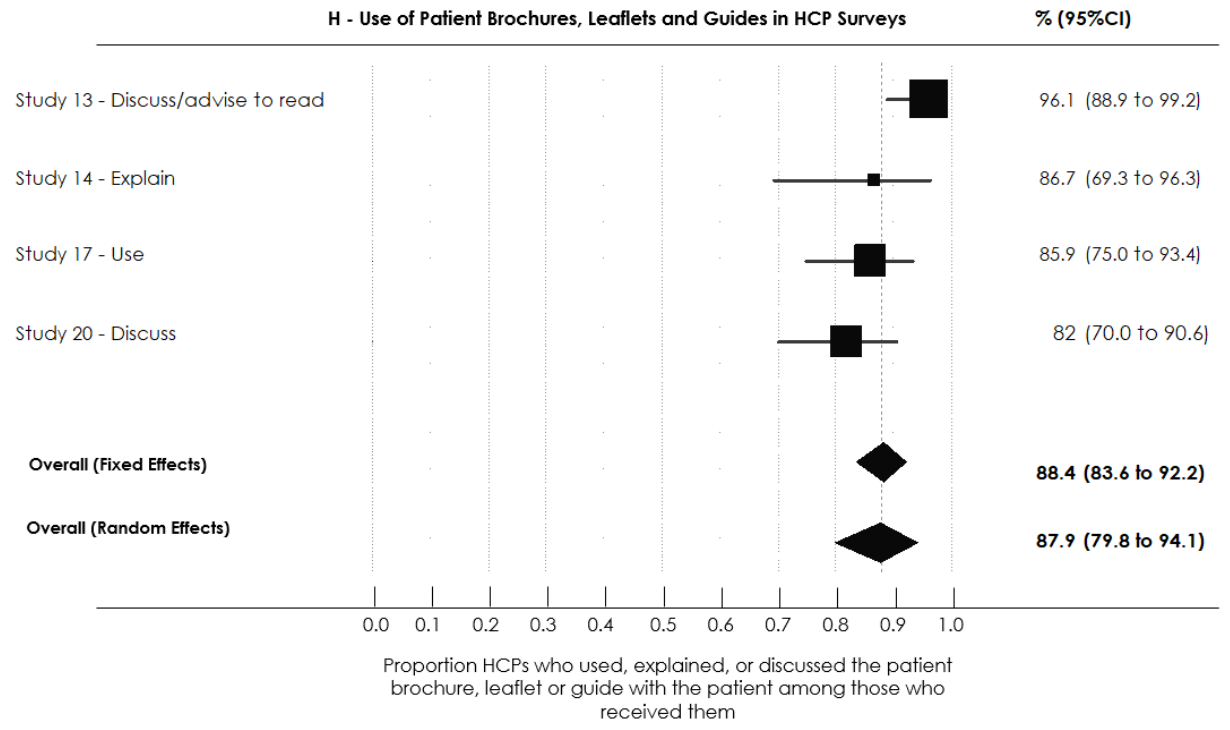


*For Study 20, response to the question 'Are you familiar with the DHPC provided to you?' was used as a proxy for receipt and therefore was included in this forest plot


E - Reading of aRMM in HCP Surveys
% (95%CI)
Study 1 - HCP Brochure
87.7 (77.2 to 94.5)
Study 2 - HCP Brochure
90.6 (86.8 to 93.7)
Study 2 - HCP Brochure
96.9 (94.2 to 98.6)
Study 14 - HCP Brochure
100.0 (88.1 to 100.0)
Study 17 - HCP Brochure
84.6 (73.5 to 92.4)
Study 20 - DHPC
73.6 (59.7 to 84.7)
Study 22 - PAC
71.7 (57.7 to 8302)
Study 23 - HCP Brochure
97.8 (94.9 to 99.3)
Overall (Fixed Effects)
92.8 (91.1 to 94.2)
Overall (Random Effects)
89.8 (82.9 to 95.1)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion HCPs who reported having read the aRMMs among those who received them


F - Use of HCP Brochures, Leaflets and Guides in HCP Surveys
% (95%CI)
Study 7 - Use
66.2 (59.7 to 72.3)
Study 8 - Wave 1 Use
73.7 (70.0 to 77.1)
Study 8 - Wave 2 Use
67.0 (62.7 to 71.1)
Study 13 - Use
78.4 (68.4 to 86.5)
Study 14 - Discuss
65.5 (45.7 to 82.1)
Study 17 - Use
78.1 (66.9 to 86.9)
Study 23 - Discuss
74.8 (68.6 to 80.3)
Overall (Fixed Effects)
71.2 (69.1 to 73.3)
Overall (Random Effects)
71.7 (67.9 to 73.3)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion HCPs who used the HCP brochures, leaflets or guides (except for Study 7 and Study 8 where receipt/awareness are not reported)


G - Use of HCP Checklists in HCP Surveys
% (95%CI)
Study 1 - Use
65.3 (53.5 to 76.0)
Study 7 - Use
68.8 (61.9 to 75.2)
Study 8 - Wave 1 Use
81.2 (77.2 to 33.8)
Study 8 - Wave 2 Use
70.5 (65.9 to 74.9)
Study 24 - Use
71.6 (64.0 to 78.4)
Overall (Fixed Effects)
73.8 (71.3 to 100.0)
Overall (Random Effects)
72.1 (66.0 to 100.0)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion HCPs who used the HCP Checklists among those who received or were aware of the material
(except for Study 7 and 8 where receipt/awareness are not reported)


H - Use of Patient Brochures, Leaflets and Guides in HCP Surveys
% (95%CI)
Study 13 - Discuss/advise to read
96.1 (88.9 to 99.2)
Study 14 - Explain
86.7 (69.3 to 96.3)
Study 17 - Use
85.9 (75.0 to 93.4)
Study 20 - Discuss
82 (70.0 to 90.6)
Overall (Fixed Effects)
88.4 (83.6 to 92.2)
Overall (Random Effects)
87.9 (79.8 to 94.1)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion HCPs who used, explained, or discussed the patient brochure, leaflet or guide with the patient among those who received them

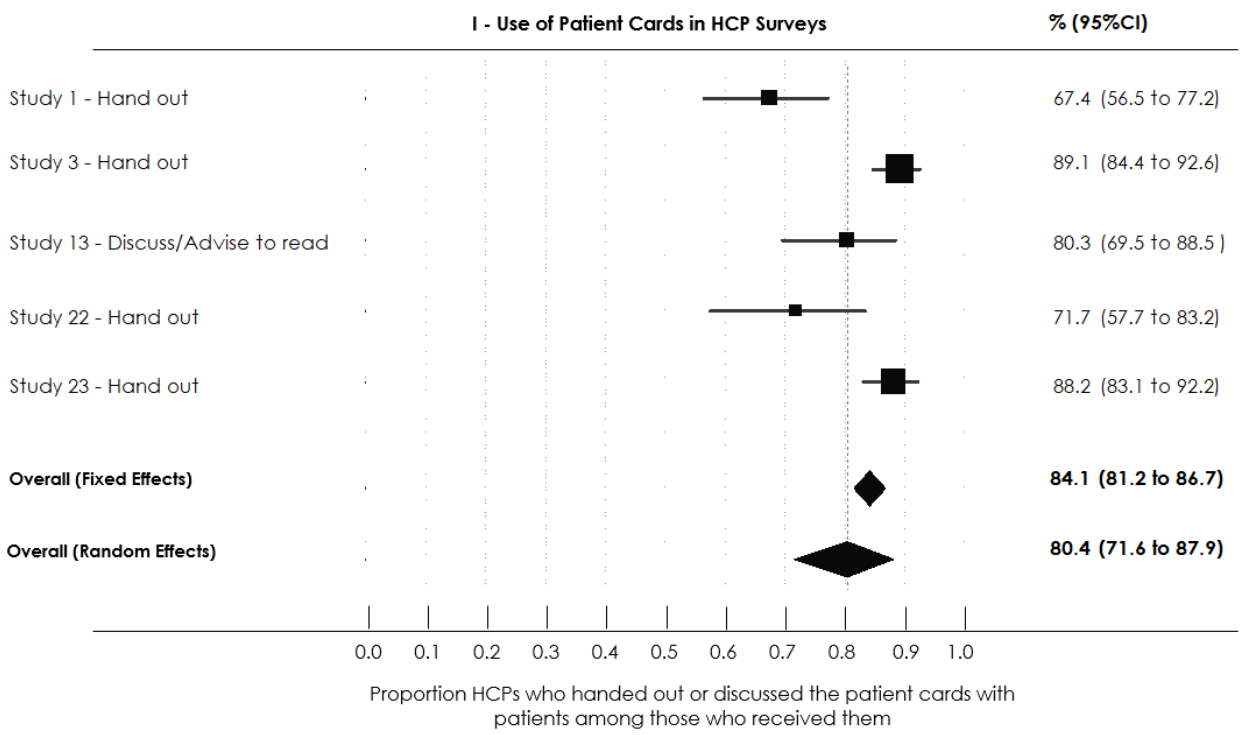
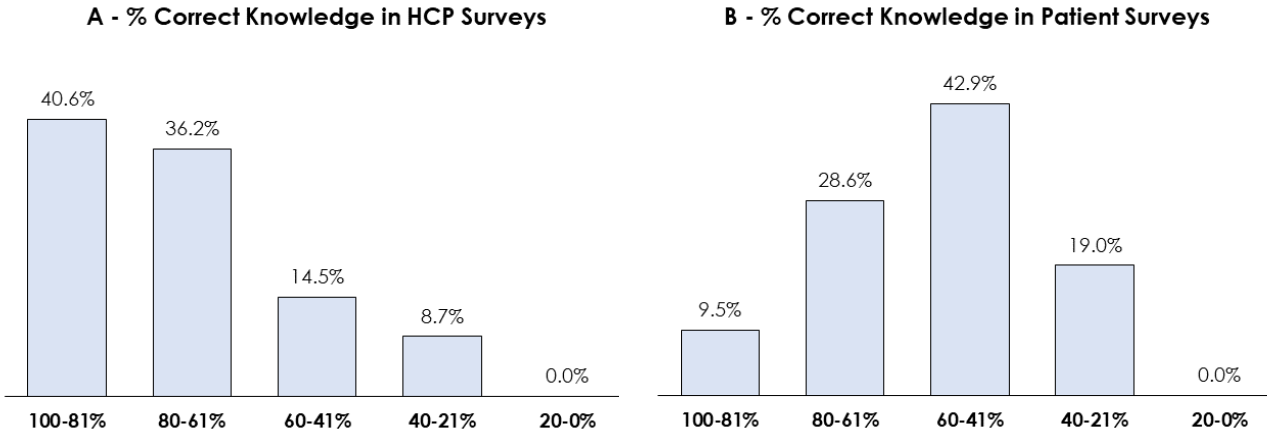


Figure 10. Receipt, Reading, and Use of aRMMs in HCP Surveys. Forest Plots A, B, C and D, respectively, represent receipt (percentage of HCPs who reported receipt) of aRMMs in HCP Surveys by aRMM type: HCP brochures, leaflets and guides; HCP checklists, Dear Healthcare Professional Communications (DHPCs); patient cards. Forest Plot E represents reading (percentage of HCPs who reported reading the materials) of HCP Brochures in HCP Surveys. Forest Plots F, G, H and I, respectively, represent use of aRMMs in HCP Surveys by aRMM type: HCP brochures, leaflets and guides; HCP checklists, patient brochures, leaflets and guides; patient cards.



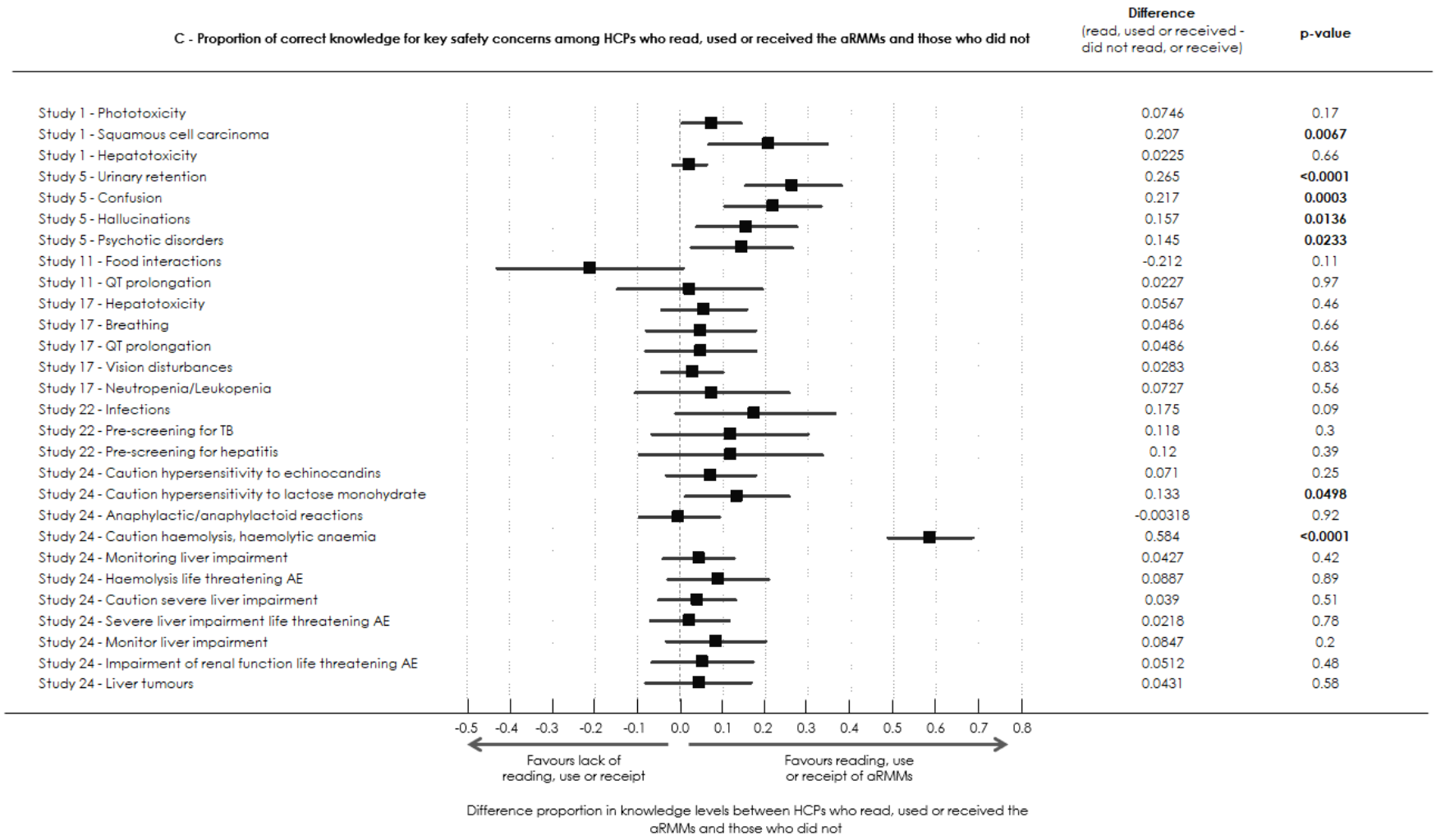
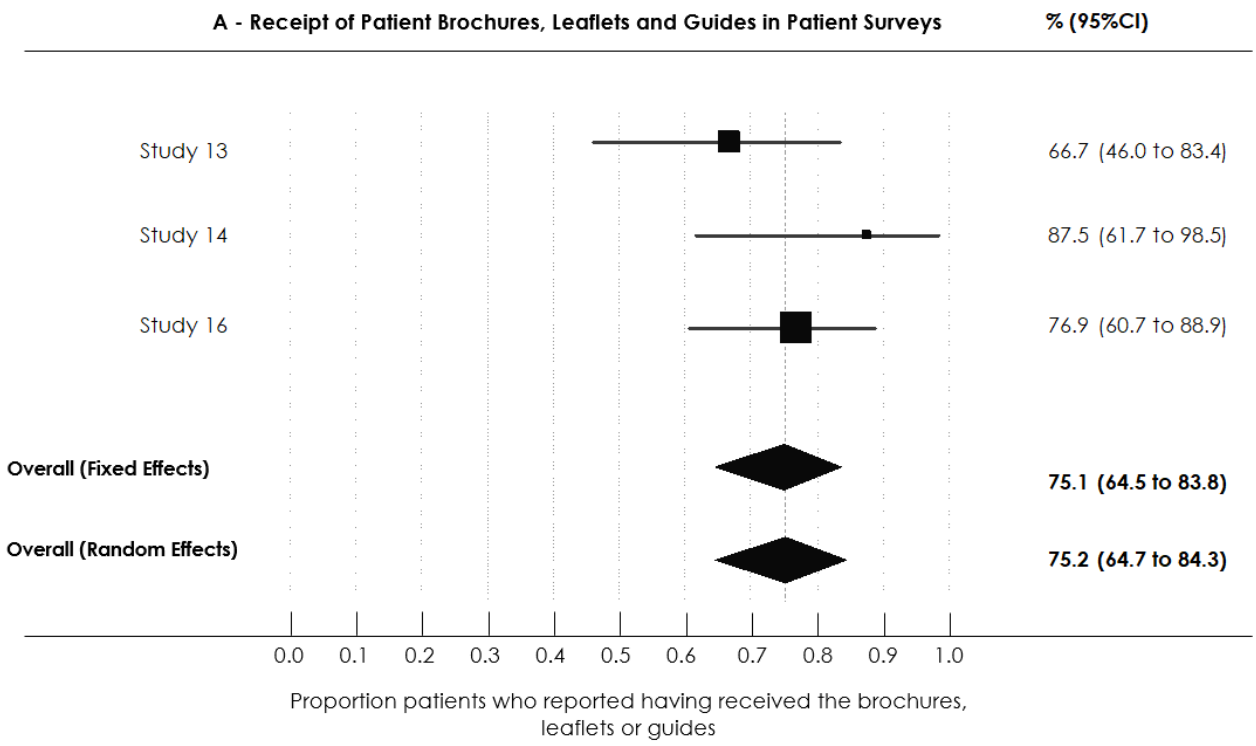


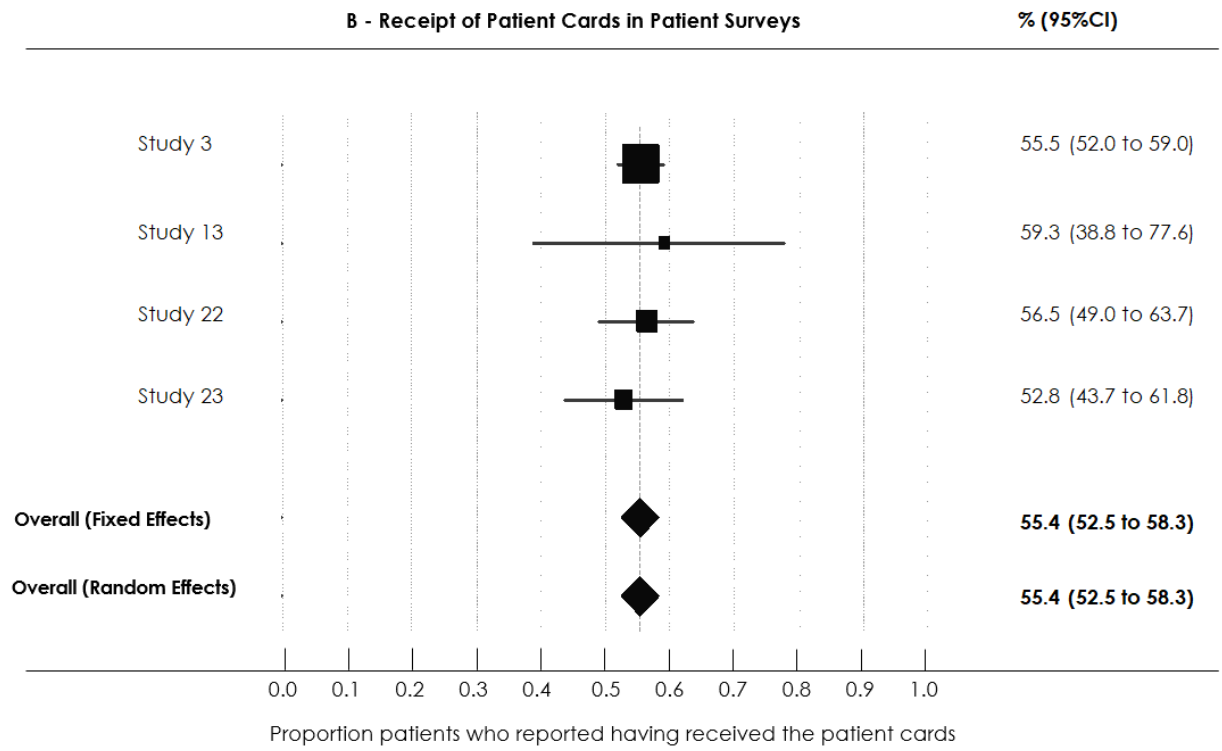
Figure 11. Knowledge of key Safety Concerns in HCP and Patient Surveys. Graphs A and B represent the distribution of knowledge results for the different key safety concerns in HCP and Patient Surveys, respectively. Forest plot C represents the level of knowledge of safety concerns in HCPs who received, read, or used the aRMMs versus those who did not.

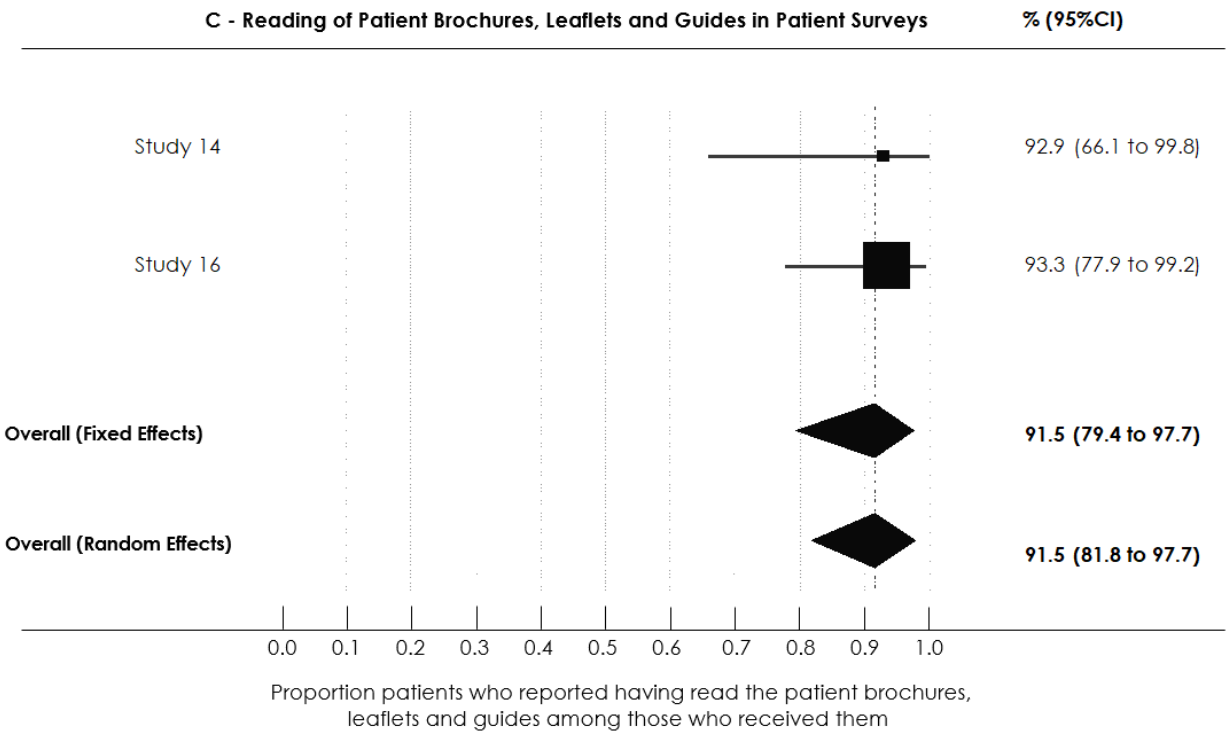
6.1.4. Patient Surveys

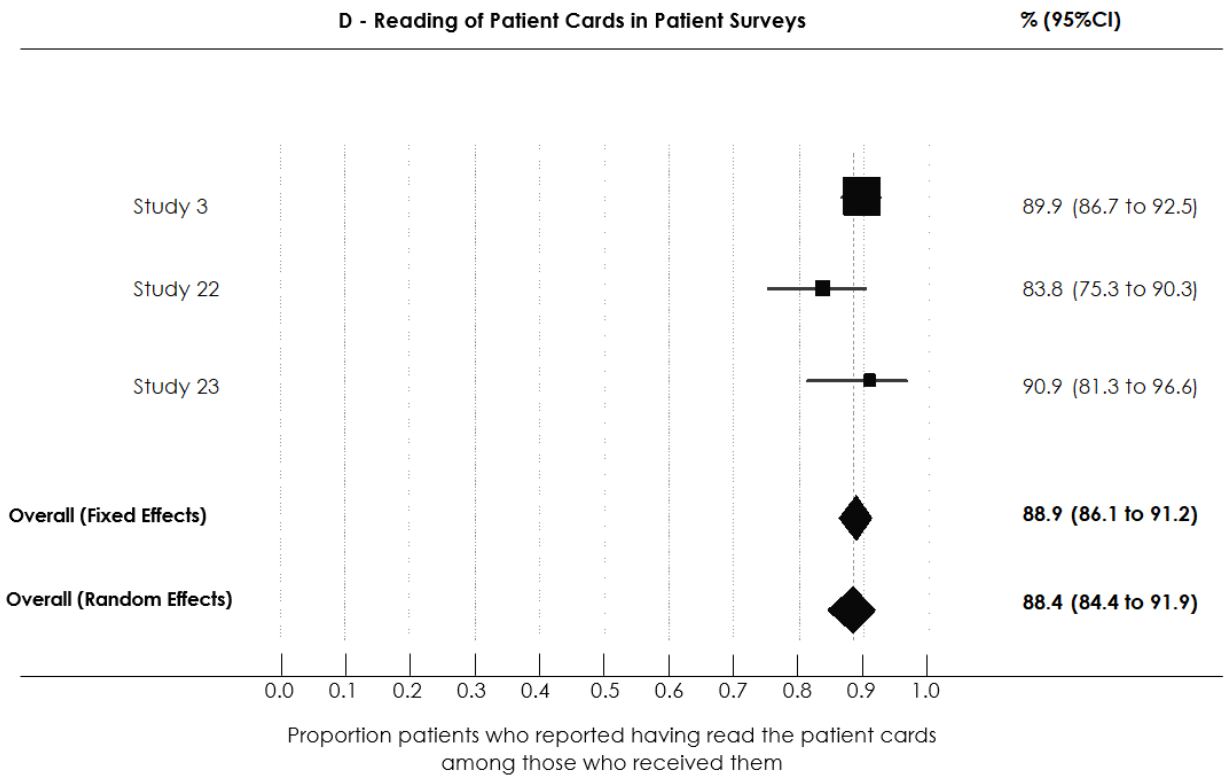
Patients and/or caregivers were included in eight of the 24 included studies. Five of the eight patient surveys did not reach the pre-specified target sample size in the study protocol. Of these five studies, one was terminated due to low recruitment and the results of one study were not reported having recruited only seven patients. The pooled 'Completers/Eligible' rate, based on 4 studies with the number of patients eligible reported, was 92.8% (I^2 = 96.5%; Figure 9 (c)). The number of patients invited was reported in only one study (Study 22), corresponding to a 'Completers/Invited' rate of 59.7%. All studies reported receipt of materials but varied in other outcomes reported: reading (5), utilization/use (4), knowledge of key safety information (6) and self-reported behaviour to implement the information (4). Receipt of materials (7 different materials) in patients ranged from 50% to 80% in six studies (Figure 12 (a,b)): 75.2% (I^2 = 12.7%) for patient brochures, leaflets or guides and 55.4% (I^2 = 0.0%) for patient cards. Figure 12 (c,d) show that all or some of the contents of the materials, among those who had received them, were read by about 90% of the patients: 91.5% (I^2 = 0.0%) for patient brochures, leaflets and guides, and 88.4% (I^2 = 36.5%) for patient cards.

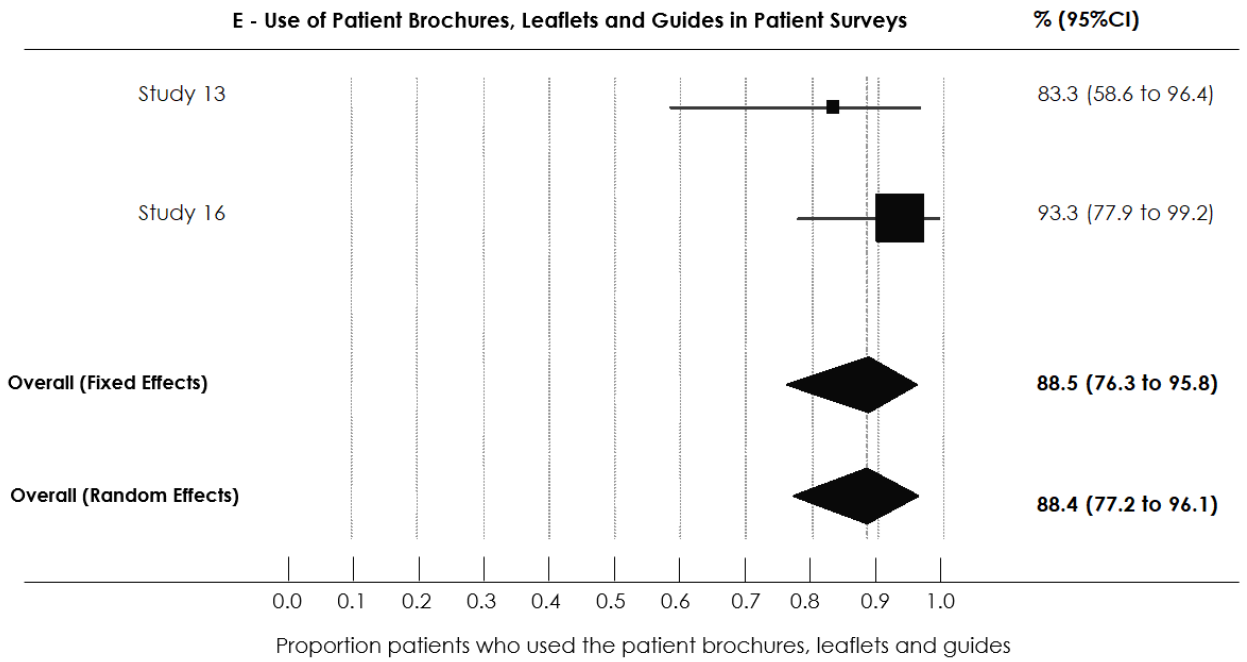
Regarding use of aRMMs (Figure 12 (e,f)) results were higher for patient brochures, leaflets, and guides, 88.4% (I^2 = 12.9%) than for patient cards, 62.6% (I^2 = 93.2%). Finally, knowledge and understanding were reported for 21 key safety concerns in six studies, 38.1% of items scoring knowledge levels >60% and 9.5% of items scoring >80% (Figure 11 (b)). Data on the implementation of behaviour resulting from aRMMs could not be abstracted and analysed due to varying ways of reporting.




B - Receipt of Patient Cards in Patient Surveys
% (95%CI)
Study 3
55.5 (52.0 to 59.0)
Study 13
59.3 (38.8 to 77.6)
Study 22
56.5 (49.0 to 63.7)
Study 23
52.8 (43.7 to 61.8)
Overall (Fixed Effects)
55.4 (52.5 to 58.3)
Overall (Random Effects)
55.4 (52.5 to 58.3)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion patients who reported having received the patient cards


C - Reading of Patient Brochures, Leaflets and Guides in Patient Surveys
% (95%CI)
Study 14
92.9 (66.1 to 99.8)
Study 16
93.3 (77.9 to 99.2)
Overall (Fixed Effects)
91.5 (79.4 to 97.7)
Overall (Random Effects)
91.5 (81.8 to 97.7)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion patients who reported having read the patient brochures,
leaflets and guides among those who received them


D - Reading of Patient Cards in Patient Surveys
% (95%CI)
Study 3
89.9 (86.7 to 92.5)
Study 22
83.8 (75.3 to 90.3)
Study 23
90.9 (81.3 to 96.6)
Overall (Fixed Effects)
88.9 (86.1 to 91.2)
Overall (Random Effects)
88.4 (84.4 to 91.9)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion patients who reported having read the patient cards among those who received them


E - Use of Patient Brochures, Leaflets and Guides in Patient Surveys
% (95%CI)
Study 13
83.3 (58.6 to 96.4)
Study 16
93.3 (77.9 to 99.2)
Overall (Fixed Effects)
88.5 (76.3 to 95.8)
Overall (Random Effects)
88.4 (77.2 to 96.1)
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Proportion patients who used the patient brochures, leaflets and guides

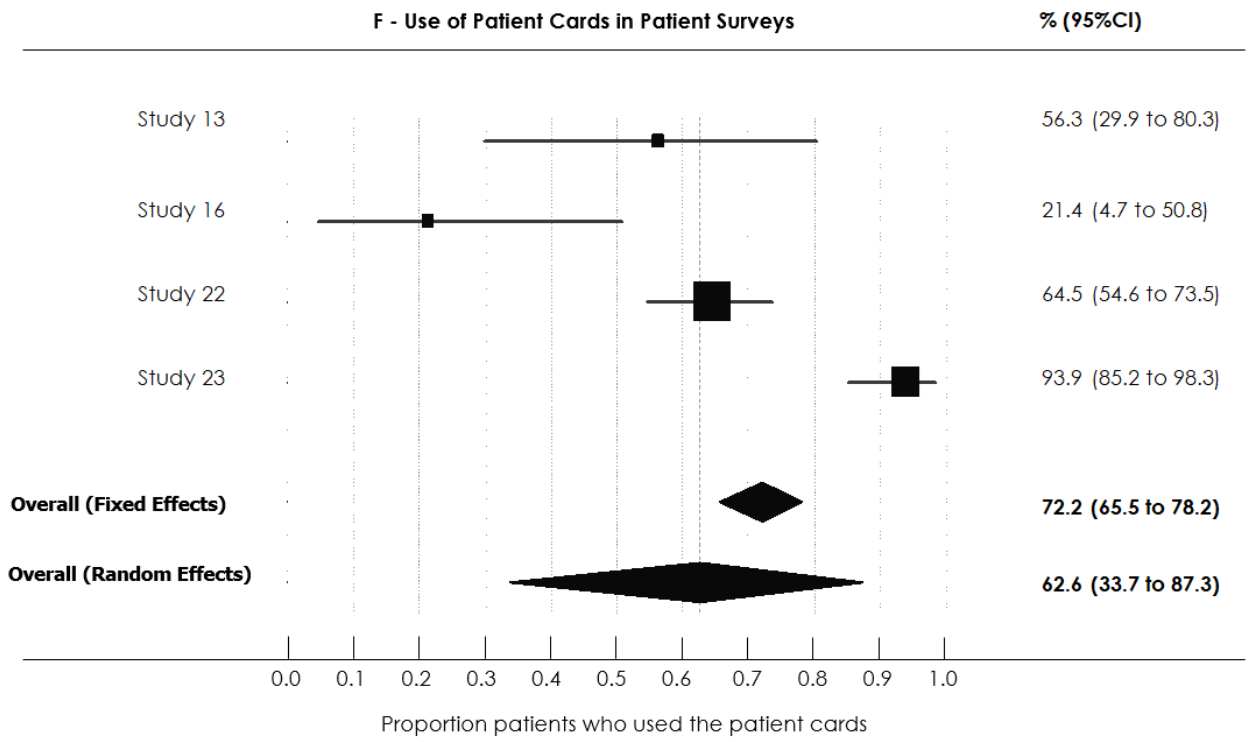


Figure 12. Receipt, Reading and Use of aRMMs in Patient Surveys. Forest Plots A and B, respectively, represent receipt (percentage of patients who reported receipt) of aRMMs in Patient Surveys by aRMM type: patient brochures, leaflets, and guides; patient cards. Forest Plots C and D represent reading (percentage of patients who reported reading the materials) of aRMMs in Patient Surveys by aRMM type: patient brochures, leaflets, and guides; patient cards. Forest Plots E and F, respectively, represent use of aRMMs in Patient Surveys by aRMM type: patient brochures, leaflets, and guides; patient cards.

6.1.5. Regulatory Submission Process & Actions taken by Regulators

Regulatory ARs were available for 22 of the 24 studies (one was not provided, and the other one was still ongoing at the time of the analysis). Table S1 describes the regulatory process for submission of study results to relevant competent authorities. Most FSRs were submitted to EMA/PRAC through a Type II variation (n=14) requiring RMP update, few were submitted at time of RMP or Periodic Safety Update Reports (PSUR) update (n=4).

Table 8 and Figure 13 show that further action was required in 59.1% (13/22) studies based on obtained ARs: improvement of distribution methods or re-distribution (31.8%), changes to the contents/format of the existing materials (18.2%), in 18.2% further data involving other studies or other data were required to determine regulatory action and follow-up assessment required in 3 studies (13.6%). Concerns about the risk of selection bias, low response rates and limited generalizability of results were raised by regulators for at least 11 of the 22 studies during the assessment process. Receipt of materials was considered to be low in at least 31.8% studies resulting in re-distribution or improved distribution

being requested. None of the studies resulted in changes to the benefit–risk balance of the medicinal products under evaluation.

Table 8. Regulatory Actions according to Assessment Reports

Regulatory Actions	**n (%) [N=24]**
Studies with Assessment Reports	22 (91.7)
Studies without Assessment Reports	2 (8.3)
Ongoing Procedure	1
Reason unspecified by national regulator	1
Main regulatory concerns	
Low response rates	7 (31.8)
Selection bias and generalizability of results	6 (27.3)
Limited receipt of materials	7 (31.8)
Regulatory Consequences	
No further action	9 (40.9)
Further action required	13 (59.1)
Improve distribution of aRMM or re-distribute	7 (31.8)
Changes to contents/format of existing aRMMs	4 (18.2)
Pending further discussion/data	4 (18.2)
Follow-up assessment requested	3 (13.6)
Removal of aRMMs	2 (9.1)
Changes to SmPC	1 (4.5)
aRMMs implemented	1 (4.5)
Re-analysis by reading/non-reading	1 (4.5)

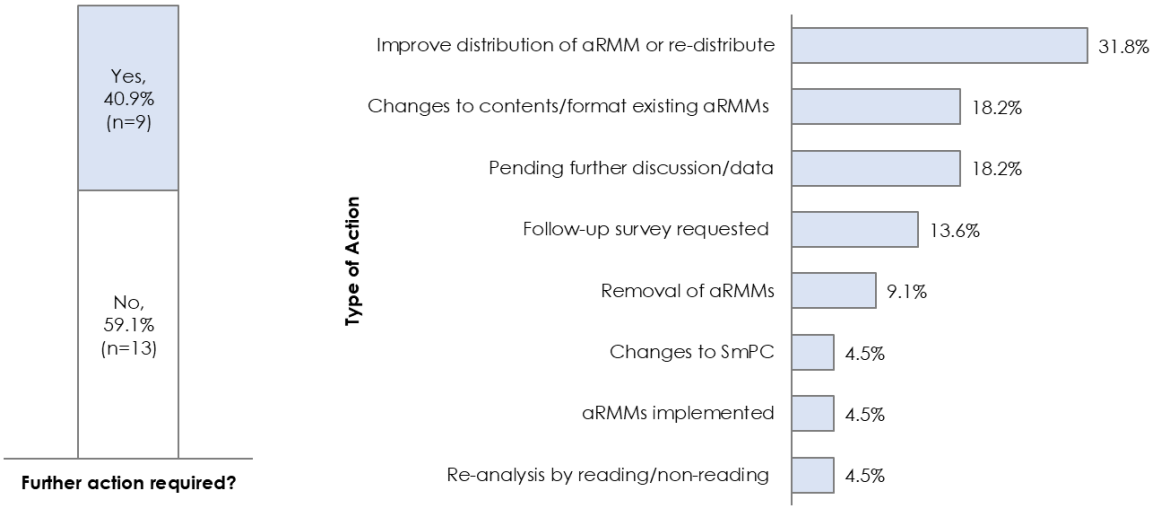


Figure 13. Regulatory Actions: if further action required (left) and type of regulatory action; multiresponse (right)

6.1.6. Summary of Study Results

The key findings show that among HCPs, the pre-specified sample size was reached in 52% of studies. Study participation was 89% defined as 'Completers/Eligible' and 5% defined as 'Completers/Invited'. Receipt of materials was recalled by up to 60% of HCPs on average. Knowledge of safety concerns was assessed, with 77% of items scoring knowledge levels >60%. Among patients and/or caregivers, the pre-specified sample size was reached in 25% of studies. Participation by patients was 93% when defined as 'Completers/Eligible' (the number of patients invited reported in only one study). Receipt of patient materials ranged between 50%-80%. Materials were read by over 90% of respondents. Overall, 38% of items scored knowledge levels >60%. Behaviour was not analyzable due to the varying formulation and reporting of survey questions. A summary of results of EU RM Survey studies is provided in Figure 14. Further action based on study results was requested by regulators in 59% (13/22) of studies, which most frequently involved re-distribution of materials or re-formulation of the existing distribution strategy.

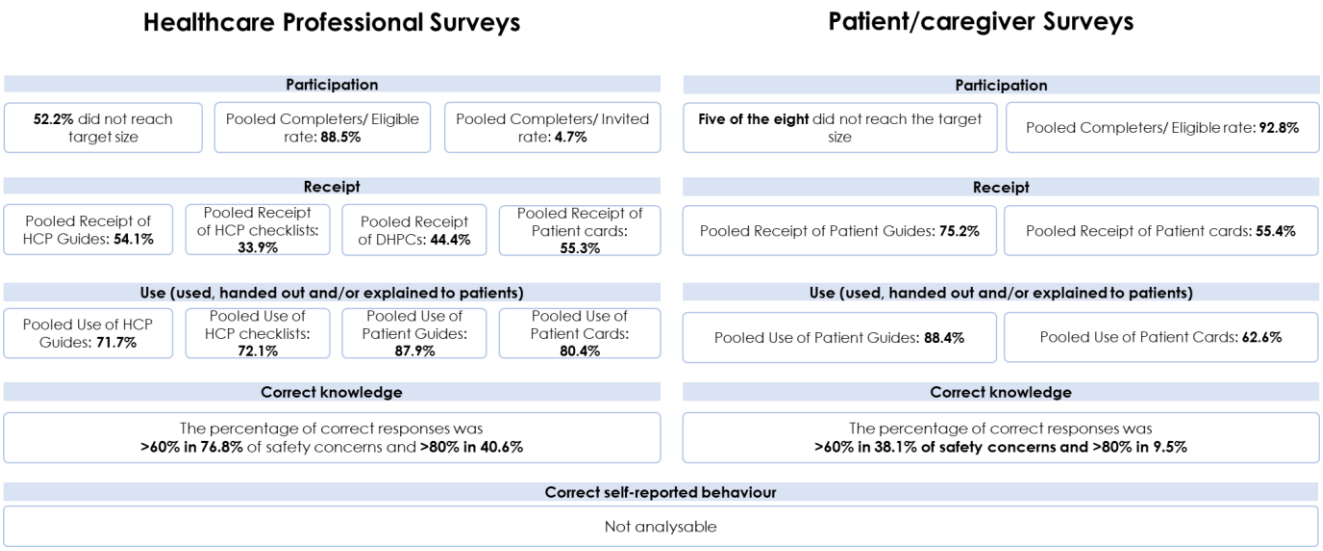


Figure 14. Key results in EU RM Surveys

6.2. Objective 2: Evaluate participation in EU RM Surveys to assess the effectiveness of aRMMs in Europe

6.2.1 Study Selection

Between 1st Jan 2012 and 12th October 2019, 129 EU RM Studies were identified, of which 92 had results available (Figure 15, according to the PRISMA Statement). Forty-eight studies had a survey component and were eligible for analysis: 44 were surveys of HCPs and 14 were surveys of patients and/or caregivers. Two additional patient surveys were identified but excluded; one was cancelled due to lack of recruitment and the other was attempted but results were not reported as only seven patients were recruited.

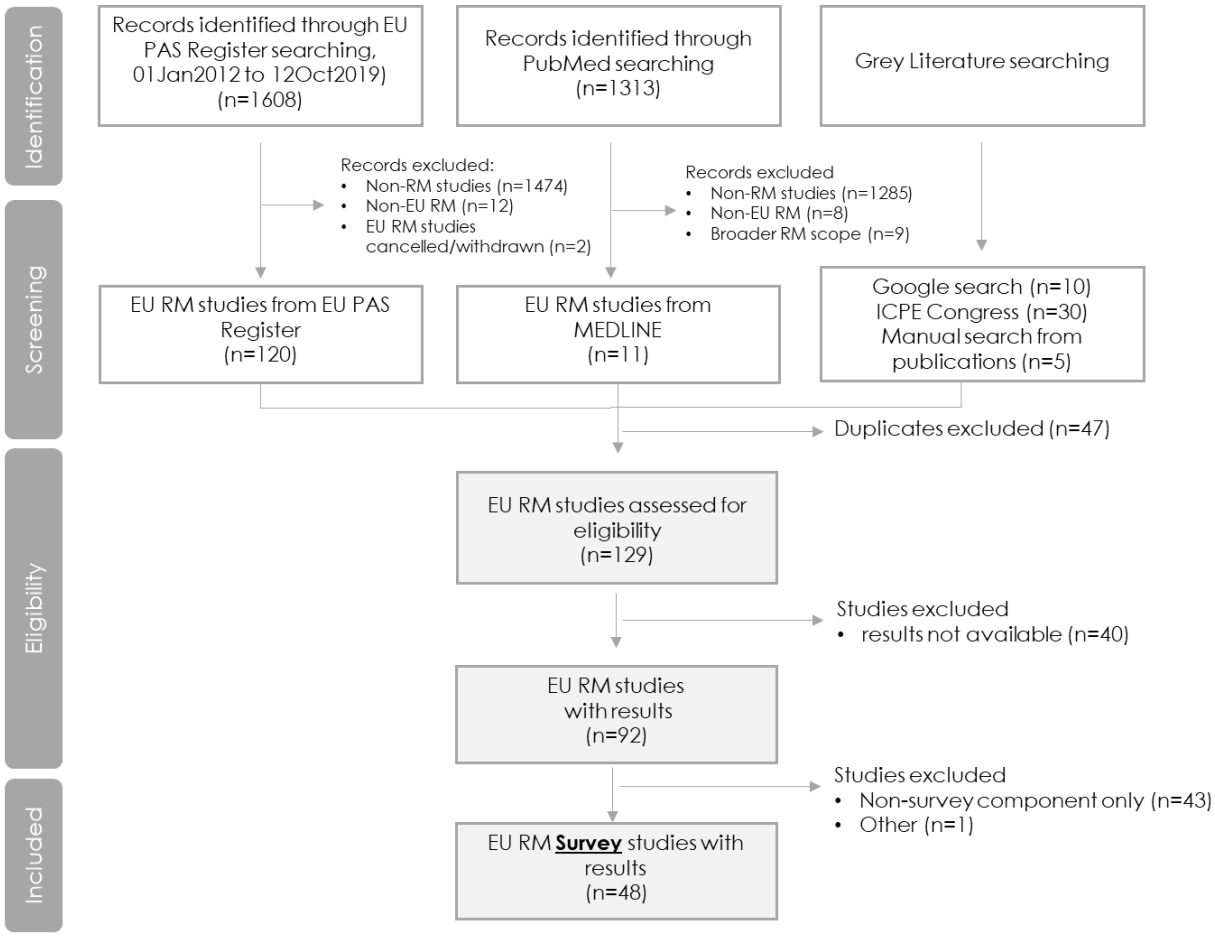


Figure 15. Flowchart of the selection process based on PRISMA guidelines – Objective 2

6.2.2 Healthcare Professional Surveys

Twenty-eight different European countries were aimed for the HCP surveys with an average of 5 (Range: 1 to 18) countries targeted per survey and 6 (Range: 1 to 18) finally participating.

The total number of HCP participants was 18207. For 17502 of them country-specific information was available.

Figure 16 shows the participation percentages in HCP Surveys by country. The most frequent countries participating in HCP surveys were the UK (33/44), Spain (28/44), France (29/44) and Germany (29/44), contributing 64.2% (by country range: 17.8% to 12.7%) of all participants with country-specific data. Italy, Sweden, Denmark, Netherlands, Belgium, and Austria participated in 18, 17, 15, 11, 10 and 10 HCP surveys, respectively, recruiting 21.5% (Range: 2.0% to 6.3%) of all participants. The other 18 countries participated in 1 to 9 studies and provided 14.3% (Ranging from 0% to 2.5%) of the HCP participants. The median HCP response rate by country ranged from 0.3% to 22.0%, being highest in Greece (22.0%), Italy (18.7%) and Czech Republic (18.4%).

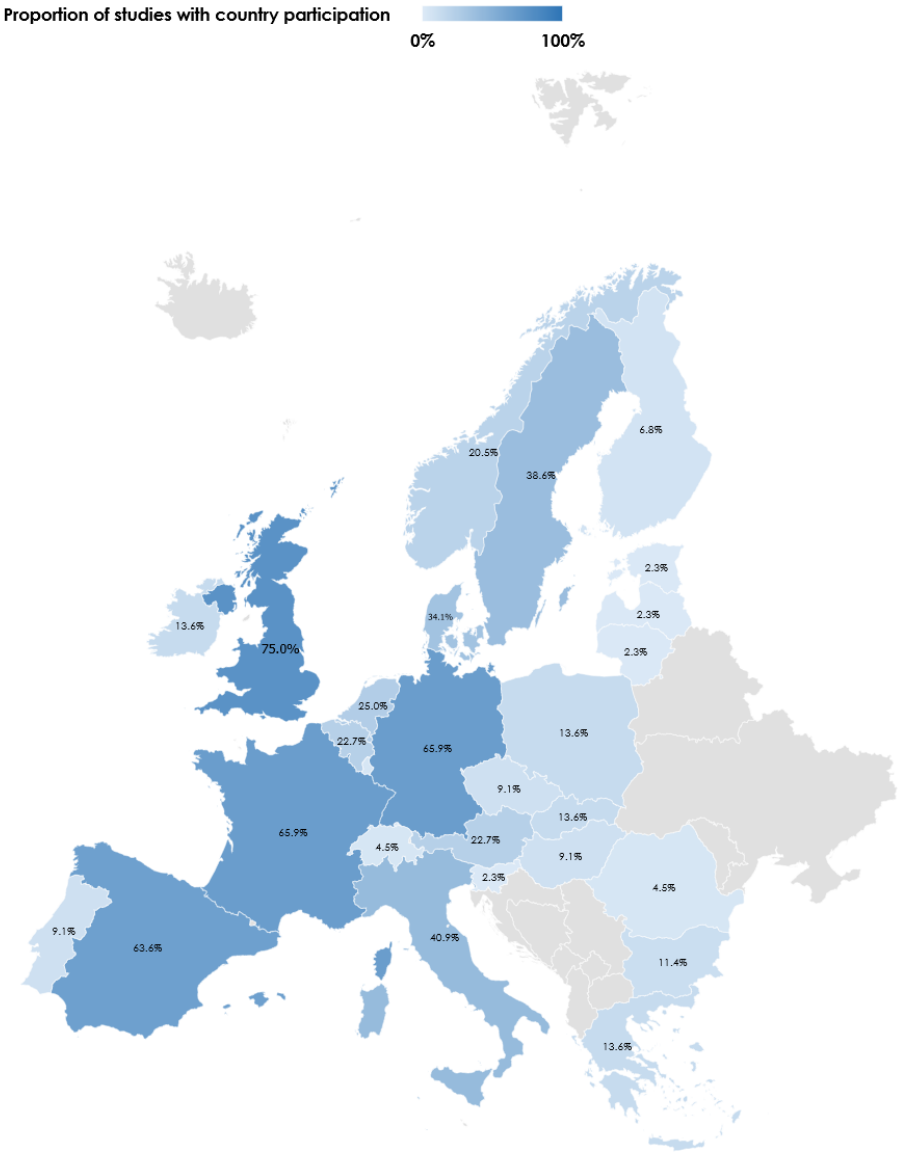


Figure 16. Map of Europe representing the percentages of participation by country in HCP Surveys

Table 9. HCP Participation Data

Country	N studies with country participation	% of participation in studies	Completers	% completers/N studies with country participation	% completers/N all studies	Range of % of participation				Range of % of response (from invited)			
						Max	Min	Med	N	Max	Min	Med	N
UK	33	75.0	3112	22.3	17.8	100.0	6.3	18.0	33	26.3	0.4	10.4	16
Germany	29	65.9	2216	17.8	12.7	33.7	4.8	14.3	29	121.7	0.3	3.2	20
France	29	65.9	2874	20.5	16.4	67.7	7.1	17.8	29	75.7	0.3	4.5	19
Spain	28	63.6	3032	20.7	17.3	57.5	9.9	19.7	28	83.3	0.8	13.7	16
Italy	18	40.9	1105	16.3	6.3	46.6	4.2	14.7	18	58.8	0.3	18.7	12
Sweden	17	38.6	767	10.5	4.4	49.3	3.1	8.3	16	30.8	2.0	3.6	8
Denmark	15	34.1	352	7.0	2.0	100.0	0.0	5.1	15	26.0	0.2	2.4	10
Netherlands	11	25.0	554	12.4	3.2	32.3	3.2	7.1	11	13.2	4.1	7.2	7
Austria	10	22.7	386	9.0	2.2	15.5	0.6	7.4	10	121.7	0.1	7.0	9
Belgium	10	22.7	601	10.4	3.4	16.1	2.0	8.4	10	16.8	6.3	8.0	5
Norway	9	20.5	112	3.2	0.6	12.2	0.0	4.1	9	2.7	0.0	0.3	5
Ireland	6	13.6	72	3.6	0.4	20.2	2.1	2.9	6	16.7	1.1	11.8	6
Greece	6	13.6	246	9.6	1.4	23.7	2.9	11.2	6	44.8	0.4	22.0	4
Poland	6	13.6	204	7.0	1.2	12.2	4.4	8.7	5	19.0	2.0	2.2	3
Slovakia	6	13.6	250.0	6.9	1.4	15.9	2.9	7.9	6	39.2	2.8	6.3	4
Bulgari	5	11.4	188	5.9	1.1	14.1	2.9	6.2	5	55.1	4.4	12.7	5
Hungary	4	9.1	205	8.0	1.2	12.5	3.9	6.5	4	64.0	3.2	15.8	4
Portugal	4	9.1	437	13.8	2.5	19.0	6.8	12.8	4	78.5	0.6	5.5	3
Czech Republic	4	9.1	266	10.5	1.5	15.8	13.9	13.9	4	24.0	12.8	18.4	2
Finland	3	6.8	79	4.4	0.5	4.5	4.4	4.4	3	6.7	6.0	6.7	3
Switzerland	2	4.5	52	7.3	0.3	7.8	6.8	7.3	2	-	-	-	-
Romania	2	4.5	185	9.6	1.1	-	-	-	-	-	-	-	-
Luxembourg	2	4.5	11	0.8	0.1	0.9	0.8	0.8	2	6.1	4.3	5.2	2
Slovenia	1	2.3	0	0.0	0.0	-	-	-	-	-	-	-	-
Estonia	1	2.3	61	5.4	0.3	-	-	-	-	-	-	-	-
Latvia	1	2.3	62	5.5	0.4	-	-	-	-	-	-	-	-
Lithuania	1	2.3	73	6.5	0.4	-	-	-	-	-	-	-	-
Others non-EU	1	2.3	2	0.5	0.0	-	-	-	-	-	-	-	-

6.2.3 Patient/Caregiver Surveys

For patient surveys, 17 different countries were involved with an average of 5.0 (Range: 3 to 10) countries targeted and participating per survey. One survey also included caregivers. The total number of patient/caregiver participants was 4129; 2996 with country-specific participation data. The UK (11/14), Germany (10/14), France (9/14) and Spain (7/14) were also the top recruiters in the patient surveys, recruiting 65.7% of all participants with country-specific data. The median patient response rate by country ranged from 90.3% to 10.0%, being highest in Spain (90.3%) and Germany (78.9%).

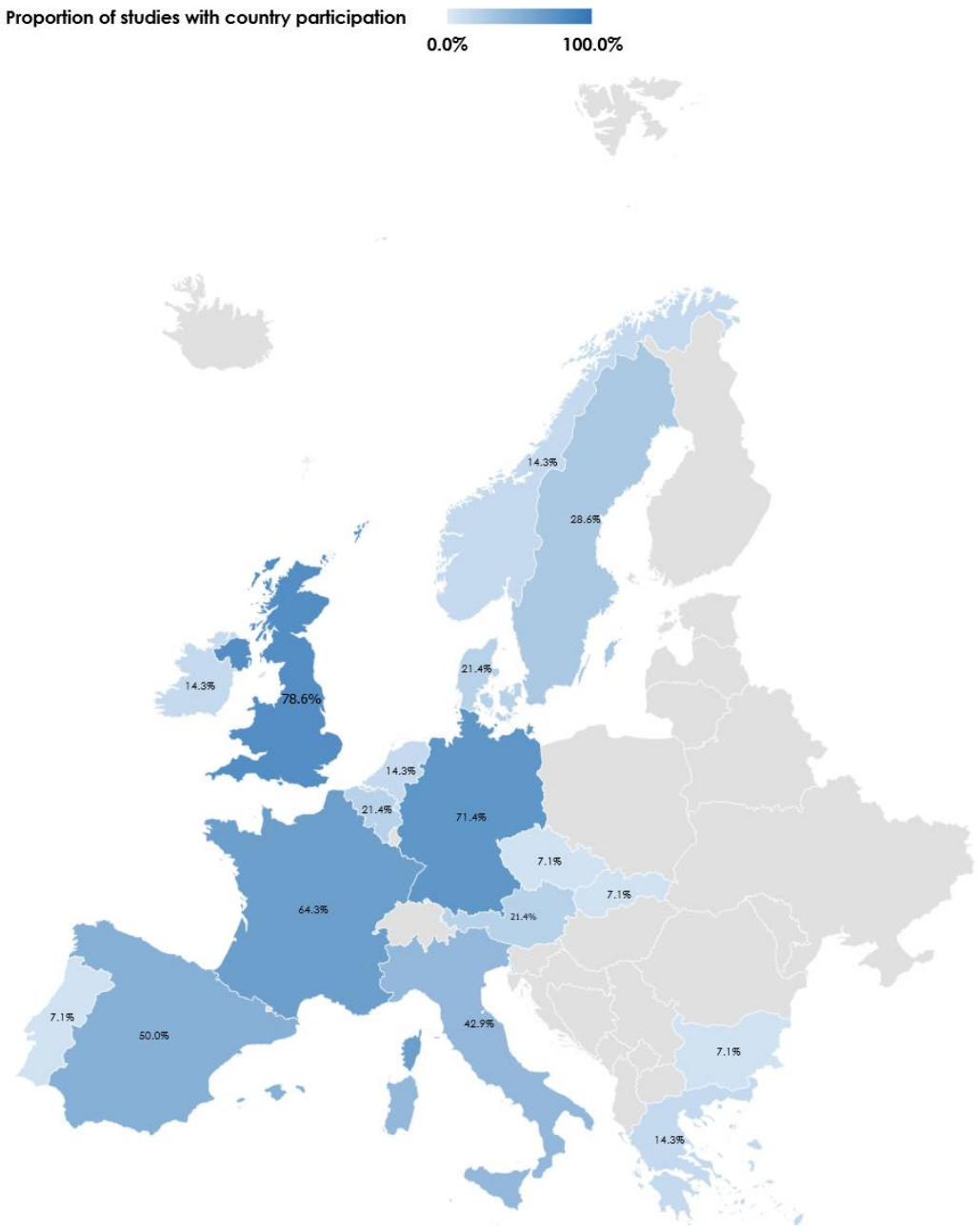


Figure 17. Map of Europe representing the percentages of participation by country in Patient Surveys

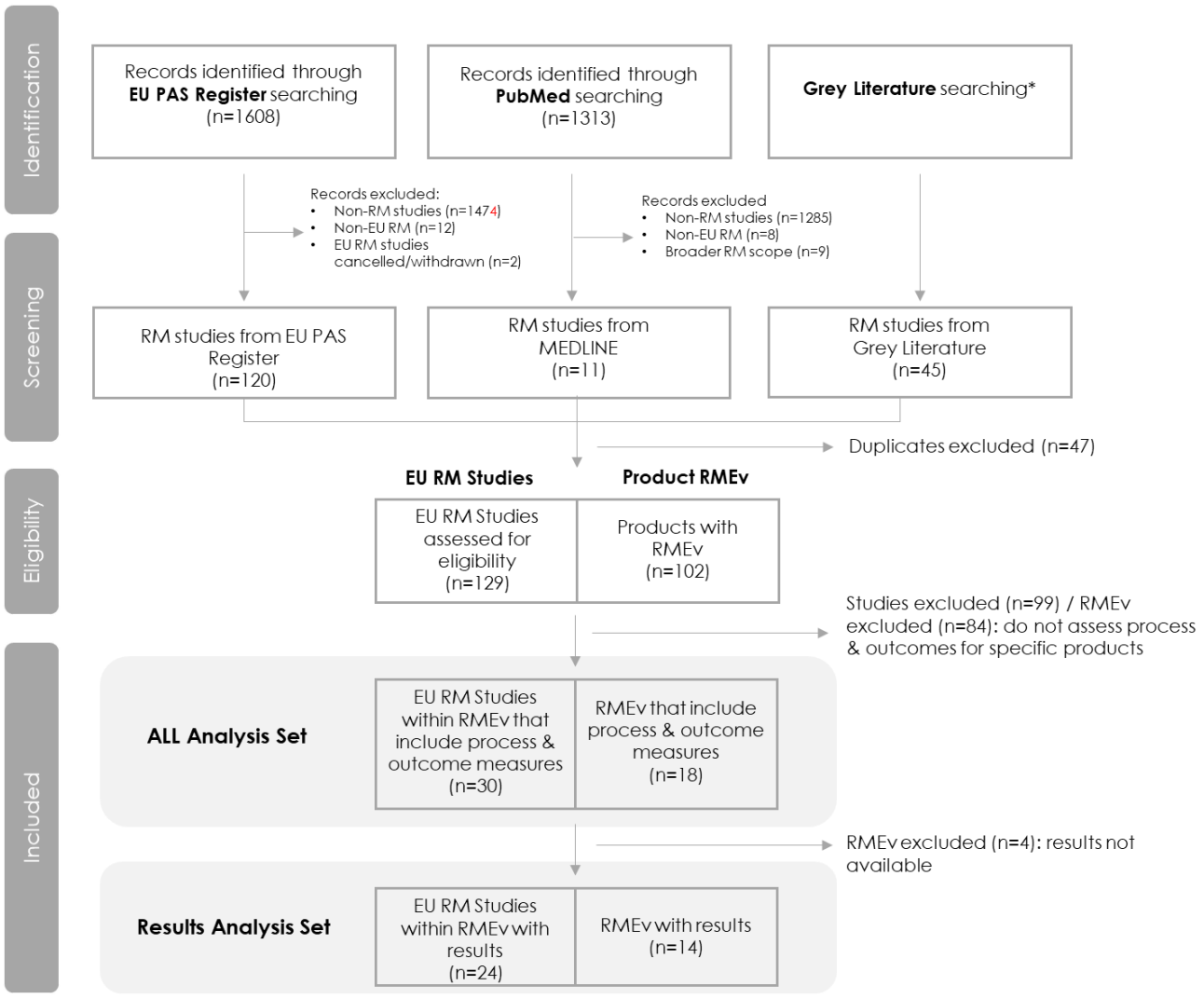
Table 10. Patient/Caregiver Participation Data

Country	N studies with country participation	% of participation in studies	Completers	% completers/N studies with country participation	% completers/N all studies	Range of % of participation				Range of % of response (from invited)			
						Max	Min	Med	N	Max	Min	Med	N
UK	11	78.6	452	14.7	15.1	31.1	0	10.3	11	57.8	57.1	57.5	2
Germany	7	71.4	426	20.4	14.2	68.8	14.3	19.7	7	100	80.6	90.3	2
France	10	64.3	750	26.6	25.0	26.4	2.3	10.7	9	100	20	78.9	3
Spain	9	50.0	339	14.2	11.3	44.2	2.6	11.5	9	64	1	42.9	3
Italy	6	42.9	285	24.46	9.5	48.8	1.6	42.2	6	34	23.6	28.8	2
Sweden	4	28.6	42	11.0	1.4	22.4	0	7.8	4	26.7	16.7	21.7	2
Austria	3	21.4	56	5.8	1.9	10.4	0	5.4	3	-	-	-	0
Denmark	2	21.4	2	3.0	0.1	3.6	2.6	3.1	2	33.3	5	19.2	2
Belgium	3	21.4	18	9.4	0.6	12.8	0	5.1	3	10	10	10	1
Ireland	3	14.3	6	3.1	0.2	12.8	0	0.8	3	11.4	11.4	11.4	1
Netherlands	2	14.3	11	7.8	0.4	8	6.3	7.1	2	-	-	-	-
Greece	2	14.3	0	0	0.0	-	-	-	-	-	-	-	-
Norway	2	14.3	269	30.1	9.0	35.5	14.9	25.2	2	-	-	-	-
Portugal	1	7.1	70	10.6	2.3	10.6	10.6	10.6	1	-	-	-	-
Bulgaria	1	7.1	59	7.4	2.0	7.4	7.4	7.4	1	-	-	-	-
Czech Republic	1	7.1	103	12.80	3.4	12.8	12.8	12.8	1	-	-	-	-
Slovakia	1	7.1	108	13.5	3.6	13.5	13.5	13.5	1	-	-	-	-

6.3. Objective 3: Systematic review of RMEv that include process indicators and outcomes

6.3.1. Study Selection Process

As of 12 October 2019, 129 studies linked to 102 products were identified (Figure 18, according to the PRISMA Statement). Eighteen products (of 102; 17.6%) had RMEv involving both process indicators and outcomes with 30 associated studies (Table S2). Of these 14 RMEv had results available, with 24 associated studies.



*Grey Literature: Google, ICPE Abstracts

ICPE: International Conference on Pharmacoepidemiology & Therapeutic Risk Management; MAH: Marketing Authorisation Holder; RM: risk minimisation; RMEv: risk minimisation evaluation

Figure 18. Flowchart of the selection process based on PRISMA guidelines – Objective 3

6.3.2. Characteristics of Products and RMEv with Process Indicators and Outcomes

The 18 products with RMEv including process indicators and outcomes were distributed among the following ATC groups: six (33.3%) antineoplastic and immunomodulating agents; five (27.8%) nervous system; two (11.1%) blood and blood forming organs; and five products (27.8%) were each from different ATC groups (Table 11). Twelve of the 18 products (66.7%) were centrally approved.

Materials targeted at HCPs were object of study in 15/18 RMEv: 12/18 (66.7%) were HCP guides, leaflets, or brochures, and 7/18 (38.9%) were DHPCs. Materials targeted at patients were evaluated in 12/18 RMEv, 10/18 (55.6%) consisting of patient cards and 5/18 (27.8%) of patient guides, leaflets or brochures. Further details about the specific aRMMs are shown in Table S2.

Table 11. Characteristics of products with RMEv involving process indicators and outcomes

	All RMEv N = 18		RMEv with Results N = 14	
	n	%	n	%
ATC Level 5				
L-Antineoplastic and immunomodulating agents	6	33.33	5	35.71
N-Nervous system	5	27.78	4	28.57
B-Blood and blood forming organs	2	11.11	2	14.29
G-Genito-urinary system and sex hormones	1	5.56	1	7.14
C-Cardiovascular system	1	5.56	1	7.14
A-Alimentary tract and metabolism	1	5.56	1	7.14
M-Musculo-skeletal system	1	5.56	0	0.00
V-Various	1	5.56	0	0.00
Type of aRMMs in RMEv				
DHPC	7	38.89	6	42.86
Patient card	10	55.56	8	57.14
HCP guide, leaflet or brochure	12	66.67	9	64.29
Patient guide, leaflet or brochure	5	27.78	4	28.57
Number of studies per RMEv				
1 study	10	55.56	8	57.14
2 studies	5	27.78	3	21.43
≥ 3 studies	3	16.67	3	21.43
Type of Outcomes				
Behavioural outcomes	12	66.67	10	71.43
Health/Safety Outcomes	9	50.00	7	50.00

Abbreviations: aRMM, additional risk minimisation measure; ATC, Anatomic and Therapeutic Class; DHPC, dear healthcare professional communication; HCP, Healthcare professional; RMEv, risk minimisation evaluation

Ten of the 18 (55.6%) RMEv included both process indicators and outcomes within the same study protocol. The involved surveys combined with a retrospective analysis of the company safety database in four RMEv, surveys combined with patient´s medical records extraction in four RMEv, one prospective study allowing for the collection of process measures (use, helpfulness) and outcomes (proportion of inappropriate prescribing), and one HCP survey assessing knowledge and self-reported

behaviour as well as reading errors. Five RMEv involved two separate studies, consisting of surveys and a drug utilisation study. Two RMEv consisted of three studies (two drug utilisation studies and a survey) and the remaining one consisted of four separate studies (three drug utilisation studies and a survey).

The proportion of RMEv that evaluated health/safety outcomes was 50.0% while 66.7% evaluated behavioural outcomes. Three RMEv evaluated process indicators, behavioural and health/safety outcomes.

Table 12 provides a listing of the RMEv included in the analysis. Table S2 provides the characteristics of each RMEv including the safety concerns addressed by the aRMMs.

Table 12. RMEv included in the analysis and main RMEv characteristics

RMEv	*Type of aRMM evaluated*					Study Ref.	Measures of effectiveness						Study Design	Data Source
							Process Indicators				Outcomes			
	HCP brochure, leaflet or guide	*DHPC*	*HCP Checklist*	*Patient brochure, leaflet or guide*	*Patient card*		Receipt	Use	Knowledge	Self-reported Behaviour	Behavioural	Health/Safety		
Quetiapine (N05A H04)	x					[71]	x	x		x			Survey	HCP Survey
						[72]					x		Retrospective Post-implementation	Databases
Cyproterone acetate /ethinylestradiol (CPA/EE) containing products (G03)		x	x		x	[73]			x	x			Survey	HCP Survey
						[74]					x		Retrospective Pre- and post-implementation	Databases
						[75,76]	x		x				Survey	HCP Survey
						[77]					x		Survey	Drug Utilisation Survey of HCPs and patients
Ipilimumab (L01XC11)	x			x	x	[78]	x	x	x	x		x	Survey	HCP and Patient Surveys
													Retrospective Post-implementation	Company Drug Safety database
Trimetazidine (C01EB15)		x				[79]	x		x	x			Survey	HCP Survey (+aggregated prescription data)
						[80]					x		Retrospective Pre- and post-implementation	Databases
						[81]					x		Retrospective Pre- and post-implementation	Databases
Domperidone-containing medicines (A03FA03)		x				[82]					x		Retrospective Pre- and post-implementation	Databases
						[83]	x		x				Survey	HCP Survey
Abatacept (L04AA24)					x	[84]	x	x	x	x		x	Survey	HCP and patient Surveys
													Retrospective Post-implementation	Medical records data
Apixaban (B01AF02)	x				x	[85]	x	x	x	x		x	Retrospective post-implementation	Company Drug Safety database
													Survey	HCP and patient Surveys

RMEv	Type of aRMM evaluated					Study Ref.	Measures of effectiveness						Study Design	Data Source
							Process Indicators				Outcomes			
	HCP brochure, leaflet or guide	DHPC	HCP Checklist	Patient brochure, leaflet or guide	Patient card		Receipt	Use	Knowledge	Self-reported Behaviour	Behavioural	Health/Safety		
Florbetapir (V09AX05)	x					**Ongoing** [86]			x	x	x		Survey	HCP Survey
Agomelatine (N06AX22)	x	x		x		[87]	x		x	x	x		Retrospective pre/post implementation	Medical records data
													Survey	Patient Survey
Rituximab (L01XC02)	x			x	x	[70,88]	x	x	x	x	x		Survey	Patient Survey
													Retrospective Post-implementation	Medical records data
Valproate and related substances (N03AG01)	x	x				[89]	x		x	x			Survey	HCP survey
						[90]					x	x	Retrospective Pre- and post-implementation	Databases
						[91]					x		Retrospective Pre- and post-implementation	CPRD
Rivastigmine (N03AG01)					x	[92]		x			x		Prospective Post-implementation	Primary data collection
Vismodegib (L01XX43)	x	x		x	x	[70]		x	x	x		x	Survey	HCP survey
													Retrospective Post-implementation	Company Drug Safety database
Trastuzumab emtansine - Kadcyla (L01XC14)	x					[70]			x		x	x	Survey	HCP feedback questionnaires
													Retrospective Post-implementation	Company Drug Safety database
Dabigatran etexilate (B01AE07)	x				x	[93]	x	x	x				Survey	HCP and Patient Surveys
						[94]					x	x	Retrospective Post-implementation	National Health Registries
Belatacept (L04AA28)					x	Ongoing [95]	x	x	x	x		x	Survey	HCP and Patient Surveys
													Retrospective post-implementation	Medical records data
Methoxyflurane (N02BG09)	x		x		x	Ongoing [96]					x	x	Prospective post-implementation	Primary data collection
						Ongoing [97]		x	x	x			Survey	HCP and Patient Surveys
Thiocolchicoside-containing products (M03BX05)	x	x		x		[98]	x	x	x	x			Survey	HCP Survey
						Ongoing [99]					x		Retrospective Pre- and post-implementation	

6.3.3. Characteristics of Studies in RMEv with Process Indicators and Outcomes

Table 13 shows the characteristics of studies included in RMEv involving process indicators and outcomes. Of the 30 studies, 63.3% (19/30) included cross-sectional surveys (47.4% targeted patients

and 89.5% HCPs), 56.7% (17/30) had retrospective components (47.1% used a pre/post assessment approach) and 10.0% (3/30) prospective designs.

Process indicators were measured in 63.3% (19/30) of studies. Receipt of aRMMs was measured in 14 of them, use of aRMMs in 12, level of knowledge in 17, and self-reported behaviour in 15.

Behavioural outcomes from existing databases were assessed via drug utilisation studies in 50.0% (15/30) of cases. The proportion of patients receiving the target drug under on-label/off-label conditions or inappropriate prescribing (over time, before and after the aRMMs or at a specific time point) was evaluated by 11 studies. Two studies evaluated medication errors, while monitoring of metabolic parameters and reading errors were assessed each by one study.

Health/safety outcomes were measured in 30.0% (9/30) of the studies and consisted of infusion-related adverse events (n=1), infections leading to hospitalisation, emergency room visits, etc. (n=2), bleeding (n=2), pregnancy exposures (n=2), hepatotoxicity and nephrotoxicity (n=1), and medication errors (n=2).

Drug utilisation and health/safety outcomes data were obtained from: existing healthcare databases (n=10), company global drug safety databases (n=4), data abstraction from medical records (n=4) or via primary data collection (n=4).

In five RMEv the correlation between process indicators and outcomes was assessed. Two studies attempted to correlate aggregate survey results with spontaneous reporting rates [78,85], two with outcomes recorded in the clinical records at an individual patient level [84,95,100], and one with prospectively collected events [96,97].

Table 13. Characteristics of Studies included in RMEv

	All Studies N = 30		**Studies with Results N = 24**	
	n	**%**	**n**	**%**
Study Design Components	***N=30***		***N=24***	
Retrospective	17	56.67	15	62.50
Time of evaluation (among retrospective)	n=17		n=15	
Post-implementation	9	52.94	8	53.33
Pre- and post-implementation	8	47.06	7	46.67
Cross-sectional Survey	19	63.33	15	62.50
Type of survey (among cross-sectional surveys)	n=19		n=15	
Patient Survey	9	47.37	7	46.67
HCP Survey	17	89.47	13	86.67
Prospective	3	10.00	1	4.17
Type of Indicator/Outcome	***N = 30***		***N=24***	
Process Indicators	19	63.33	15	62.50
Type of Process Indicators				

	All Studies N = 30		Studies with Results N = 24	
	n	%	n	%
Receipt	14	46.67	11	45.83
Use / usage / usefulness (reading/distribution)	12	40.00	8	33.33
Knowledge	17	56.67	13	54.17
Self-reported Behaviour	15	50.00	10	41.67
Behavioural Outcomes e.g. Drug utilisation	15	50.00	13	54.17
Type of Drug Utilisation Measures				
Off-label / on-label use / inappropriate prescribing	11	40.00	10	41.67
Monitoring metabolic parameters	1	6.67	2	8.33
Reading errors	1	3.33	0	0.00
Medication errors	2	6.67	1	4.17
Health/Safety Outcomes	9	30.00	7	29.17
Type of Health/Safety Outcomes				
Infusion related adverse events	1	3.33	1	4.17
Infections (leading to hospitalisation, emergency room visits, etc.)	2	6.67	1	4.17
Bleeding	2	6.67	2	8.33
Pregnancy exposures	2	6.67	2	8.33
Medication errors	2	6.67	1	4.17
Hepatotoxicity, nephrotoxicity	1	3.33	0	0.00
Behavioural and/or Health/Safety Outcomes	21		17	
Data Source				
Company Global Drug Safety databases	4	19.05	4	23.53
Healthcare Databases	10	47.62	8	47.06
Medical records data extraction	4	19.05	3	17.65
Primary data collection	4	19.05	2	11.76

Abbreviations: HCP, Healthcare professional; RMEv, risk minimisation evaluation

6.3.4. Results of Studies in RMEv involving Process Indicators and Outcomes

Results were available for 14/18 products with RMEv (characteristics presented in Table 11), involving 24 separate studies (characteristics presented Table 13).

6.3.4.1. Results of Process Indicators

Table 14 shows the summary results of process indicators.

Of the 17 HCP survey studies in this review, 13 had results available. Data on receipt were available in nine studies, with a median of 57% (Range: 16% to 96%) respondents reporting having received the materials. Among recipients, the median proportion of respondents reading the materials, based on five studies, was 92% (Range: 72% to 98%) and for respondents using the materials, based on six studies, the median was 80% (Range: 68% to 97%). The median percentage of HCPs responding correctly to knowledge questions about key safety concerns was 77% (Range: 26% to 100%), while behaviour implementation was correctly indicated by 74% (Range: 0% to 96%) of respondents.

Of the nine patient survey studies in this review, seven had results available. Data on receipt were available in six studies, with a median of 56% (Range: 30% to 67%) respondents reporting having received the materials. Among recipients, the median of respondents reading the materials, based on four studies, was 87% (Range: 80% to 91%) and the median of respondents using the materials, based on four studies, was 65% (Range: 38% to 94%). The median percentage of patients responding correctly to knowledge questions about key safety concerns was 47% (Range: 22% to 73%), while behaviour implementation was correctly indicated by a median of 69% (Range: 42% to 96%) of respondents.

No statistically significant differences were found for receipt, reading or behaviour between HCP and patient survey studies. Significantly better results ($p < 0.05$) were observed for use and knowledge acquired in HCPs compared to patients with the Kolmogorov-Smirnov test, while only knowledge was found statistically significant ($p < 0.05$) with Mann-Whitney U test.

Table 14. Summary of results of process indicators

	Receipt of the aRMM	Reading the aRMM [a]	Use of the aRMM [a]	Correct Knowledge of Key Safety Risk	Correct Self-reported Behaviour around Key Safety Information
HCPs					
Studies with results (n)	9	5	6	9	7
Indicators (n)	15	6	9	29	23
Median (%)	56.9	91.8	80.3	77.1	74.0
Max. (%)	96.2	97.8	97.2	100.0	96.0
Min. (%)	16.2	71.7	68.0	25.8	0.0
Patients					
Studies with results (n)	6	4	4	6	4
Indicators (n)	7	4	5	13	11
Median (%)	56.0	86.9	64.5	47.4	69.0
Max. (%)	66.7	90.9	93.9	72.6	96.0
Min. (%)	30.0	79.6	37.9	22.2	42.0
p-value*	0.253	0.176	0.032	0.005	0.390
p-value**	0.458	0.454	0.161	0.002	0.768

a. Among those who received the materials
* Non-parametric test-Kolmogorov-Smirnov
**Non-parametric test-Mann-Withney U test
Abbreviations: aRMM, additional risk minimisation measure; HCP, healthcare professional

Results of process indicators within each RMEv are displayed in Table S3.

6.3.4.2. Results of Behavioural and/or Health Outcomes

Ten RMEv (involving 13 studies) reported results of behavioural outcomes and seven (involving 7 studies) reported results of health/safety outcomes. Main results are summarised in Table 15 and Table S4, respectively.

Among the 13 studies with results reporting behavioural outcomes, two assessed compliance with recommendations on performance of monitoring tests [72,87]. One reported an increase in performance of liver tests from the pre-implementation period with a median of 27.6% (Range: 15.1% to 56.3%) patients compliant with recommendations to a median of 42.3% (Range: 16.3% to 67.2%) post-implementation of the measures [87]. The other study evaluated performance of a range of monitoring tests with results that differed substantially between the two participating countries [72]; median of 33.2% (Range: 27.7% to 55.6%) of patients being monitored in the UK and 0.6% (Range: 0.0% to 6.9%) in Germany.

Ten studies evaluated the proportion of off-label use and/or inappropriate prescribing, four of which reported this proportion after the implementation of measures. In one study, 34.5% of patients were prescribed cyproterone acetate/ethinylestradiol in accordance with the updated label [77]. The prescription of inappropriate doses of dabigatran to patients >75 years decreased from 34.5% to 15% a year after the safety update [94]. Valproate prescribing in women 14-45 years decreased 17% from 2015 to 2010 after strengthening recommendations in the UK [91]. In another study [88] the median proportion of patients prescribed rituximab for off-label indications across the five participating countries was 29.9% (Range: 16.5% to 43.4%).

Five studies evaluated changes in off-label/inappropriate use before–after the implementation of aRMMs, with declines in median proportions across countries noted in two studies (from 33.6% to 27.6% [77] and from 28% to 18% [92]) and moderate improvements in compliance with all label requirements reported by another study [82]. In the two studies with trimetazidine, changes in proportion of prescriptions diverged across countries [79,81]). One additional study [74] only had interim pre-implementation results available at the time of this review.

Among seven studies reporting health/safety outcomes, two provided the number of spontaneously reported cases within a reporting period [70], with no cases of the event of interest being reported. Two studies evaluated changes in number of cases over time; while one observed a decrease in pregnancies exposed to valproate after the implementation of measures [90], the other did not find a clear trend over time [94]. The remaining three evaluated the correlation of survey responses with the occurrence of the health/safety outcome of interest at different levels (i.e., correlation of aggregate results versus within patient correlation). From the two studies that correlated aggregate survey responses with reporting rates from safety databases [78,85], one reported no correlation between survey aggregated results (patients/HCPs) and adverse drug reactions in any combination (overall sample and per indication) which only turned positive among patients when outlier data

points were removed from the analysis [85]. The study that correlated survey results with the event of interest in the same patients who completed the survey [84] reported a numerical trend in the reduction of events as the level of understanding and implementation of measures from the survey increased. However, due to the small number of events the correlation was not statistically significant. The three studies mention caution in the interpretation of the findings due to methodological limitations (e.g., small number of patients, spontaneous reporting rates, and ecological correlations).

Table 15. Summary of results of health/safety outcomes

Product / RMEv	Study Ref	Outcomes	Results
Ipilimumab	[78]	Correlation between ability to respond to (any) risk scenarios in the survey and the total or organ-specific injection related adverse reactions reporting rates per country	No correlation between ability to respond to (any) risk scenarios and total or organ-specific injection related adverse reactions reporting rates per country; or between the use of RM tools and total injection related adverse reactions reporting rates per country.
Abatacept	[84]	Correlation between the global score of understanding and implementation of the patient alert card from patient survey and the number of infections leading to hospitalisation, retrospectively collected from patient medical records	The percentage of patients with infections leading to hospitalisation increased as the global score of understanding and implementation of the patient alert cards (from the patient survey) decreased: 3% for scores ≥ 67%, 5% for scores 34-67% and 8% for scores 0-33%. However, with few patients experiencing infection, the correlation was not statistically significant.
Apixaban	[85]	Correlation between survey aggregated results of knowledge and behaviour and spontaneously reported preventable bleedings per country	The analysis of scatter plots and correlation coefficients suggested no correlation between survey aggregated results (patients/HCPs) and ADR cases in any combination (overall sample and per indication). After removing influential data points from the analysis, there was evidence to support a correlation between overall patient/caregiver knowledge and the proportion of potentially preventable bleeding ADRs per country. This finding should be interpreted with caution since the analysis explored ecological correlations rather than individual correlations
Valproate and related substances	[90]	Changes in pregnancy exposure before-after the implementation of the measures	Overall, 923 pregnancies including 451 exposed to valproate (48.9%) from the entire pre-implementation period and 350 including 182 exposed to valproate (52.0%) from the entire post-implementation period were identified in the target countries. In Sweden and UK, providing the most interpretable pregnancy data in this report, the incidence rate of pregnancies exposed to valproate decreased from 0.0095 to 0.0080 per 12 person-months and from 0.0169 to 0.0109 per 12 person-months, respectively.
Vismodegib	[70]	Number of spontaneously reported pregnancy cases exposed to the drug in a reporting period	No pregnancy cases had been reported, either from maternal or paternal exposures
Trastuzumab emtansine	[70]	Number of spontaneously reported medication error reports of product confusion in a reporting period	There were 24 medication error reports in this period for which 8 were from the EU, but none from UK (from a global cumulative market exposure of 6519 patients). Product confusion with Herceptin was not reported for any.
Dabigatran	[94]	Trend in quarterly proportion of the total number of patients treated with dabigatran and experiencing major bleedings over time	Ranged from 0 to 0.5% of incident users with no clear trend over time.

6.4. Objective 4: Case Study to evaluate the effectiveness of aRMMs linking process indicators and outcomes

6.4.1. Patient Population

The disposition of patients is presented in Figure 19.

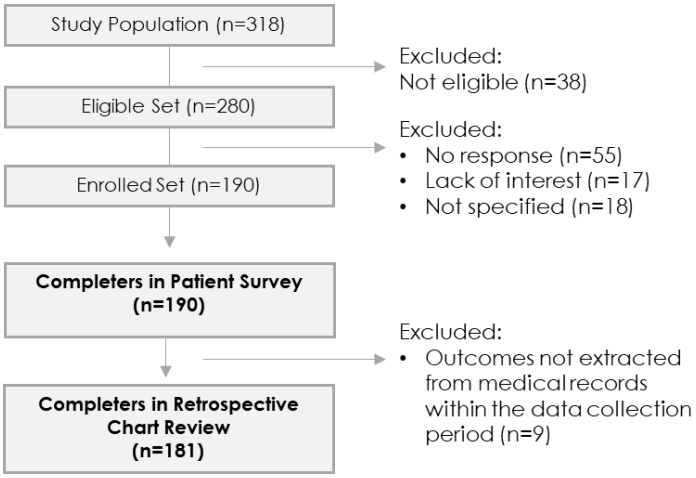


Figure 19. Study population in patient survey and retrospective chart review – Objective 4

Participation rates calculated were: 59.7% (190/318) by completers/invited and 67.9% (190/280) by completers/eligible.

6.4.2. Patient Survey

6.4.2.1. Patient Characteristics

The characteristics of patients in the survey are summarised in Table 16. The distribution of participants among the participating countries was: 39.5% (75/190) in Spain, 31.1% (59/190) in the UK, 15.8% (30/190) in Germany, 8.4% (16/190) in France and 5.3% (10/190) in Sweden. Patients were mainly aged > 55 years (70.5%, 134/190) and female (76.8%, 146/190). The majority of patients had been on Abatacept for > 1 year (66.5%, 125/188) at the time of completing the survey, followed by 7-12 months in 29/188 (15.4%) of cases. Abatacept was administered largely subcutaneously (66.1%, 125/189), with the patient being the primary administrator (53.4%, 101/189). Patients were poly-medicated; 72/188 receiving 5-8 medicines (38.3%), 67/188 receiving 2-4 (35.6%) and 38/188 receiving more than 8 (20.2%). A minority were on monotherapy with Abatacept (5.3%, 10/188).

Table 16. Patient Characteristics

	Patients N=190
Country	n (%)
France	16 (8.42)
Germany	30 (15.79)
Spain	75 (39.47)

	Patients N=190
UK	59 (31.05)
Sweden	10 (5.26)
Type of Questionnaire	
Paper	169 (88.95)
Electronic	21 (11.05)
Age group	
18-25 years	0 (0.00)
26-35 years	6 (3.16)
36-45 years	21 (11.05)
46-55 years	29 (15.26)
56-65 years	55 (28.95)
> 65 years	79 (41.58)
Gender	
Male	44 (23.16)
Female	146 (76.84)
Educational level	
No schooling completed	12 (6.38)
Primary school	42 (22.34)
No schooling completed/ Primary school	0 (0.00)
Secondary school	81 (43.09)
Some college further education (e.g., at a college)	24 (12.77)
Bachelor's degree	8 (4.26)
Master's degree or doctorate	15 (7.98)
Other professional qualification	6 (3.19)
Missing	2

6.4.2.2. Patient Survey Results

From those with information, 59.7% (111/186) of patients were aware of the PAC, of whom 94.6% (105/111) recalled having received or accessed it, mainly through the specialist nurse (44.8%, 47/105) and in the medication box (30.5%; 32/105); and 83.8% (88/105) had read the material. By route of administration, 65.6% (40/61) of patients were aware of the PAC for the IV formulation and 56.9% (70/123) for the SC formulation.

More than half the patients who received the PAC or selected 'I do not remember' (56.6%; 60/106) indicated that the information contained in the material had been explained to them. Among 76 patients who received explanation of the contents of PAC or who selected 'I do not remember', the source of the explanation was primarily a specialist nurse for 53.9% and a doctor in 35.5%.

The PAC was *carried at all times* by 64.5% (69/107) of patients and 59.6% (62/104) were aware that they should present it to every physician involved in their healthcare. The mean scores were (SD): 65.2% (29.5) for utilization, 87.2% (22.7) for understandability, 65.5% (42.3) for clarity, 64.2% (41.8), for conciseness, 61.1% (40.2) for completeness, 56.3% (42.3) for brevity, resulting in an overall mean utility score of 60.5% (32.8). A graphical representation of the scores is provided in Figure 20.

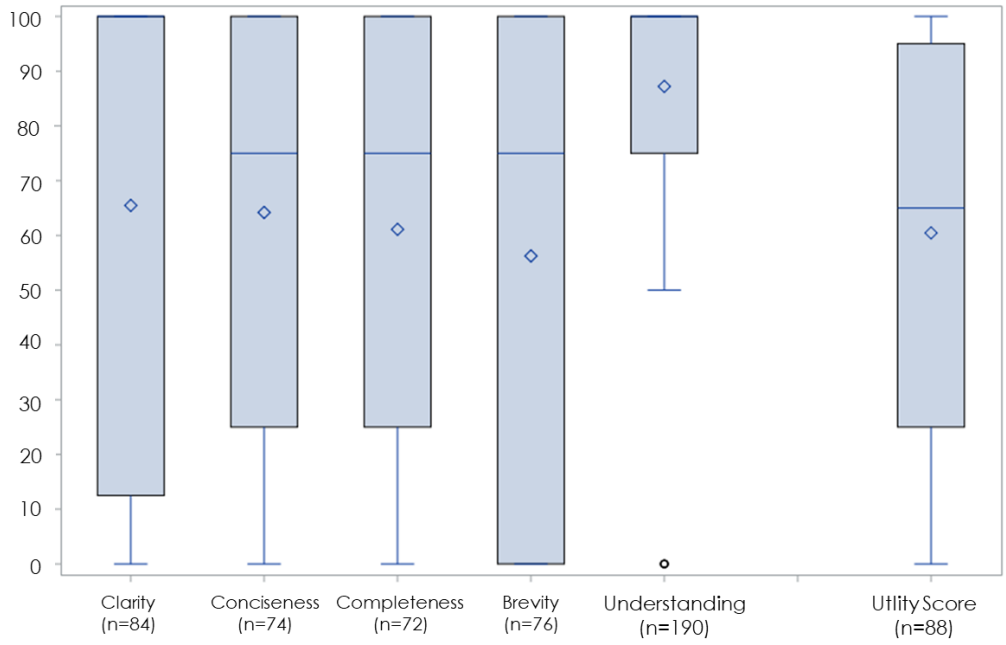


Figure 20. Clarity, conciseness, completeness, brevity, and understandability of the PAC in the patient survey

Levels of correct knowledge in patients is shown in Figure 21. The mean knowledge score (across all knowledge questions) was higher among those who recalled receiving the PAC compared to those who did not (64.5% vs 36.9%; $p<0.001$). As shown in Figure 22, knowledge about the risk of infections was higher among those who recalled having received the PAC compared to those who did not (63.8% vs 45.9%; $p=0.013$). Knowledge about pre-screening for TB and VH were correctly indicated by 77.9% and 47.4% of patients, respectively. In both cases, this knowledge was among those who recalled having received the PAC compared to those who did not: 87.6% vs 65.9% for TB ($p<0.01$) and 55.2% vs 49.2% for VH ($p=0.016$). While only 28.4% of patients identified the PAC as a source where to find information about the benefits and risks of abatacept, it was higher among those who recalled receiving the PAC than those who did not (35.2% vs 26.2%; $p=0.021$).

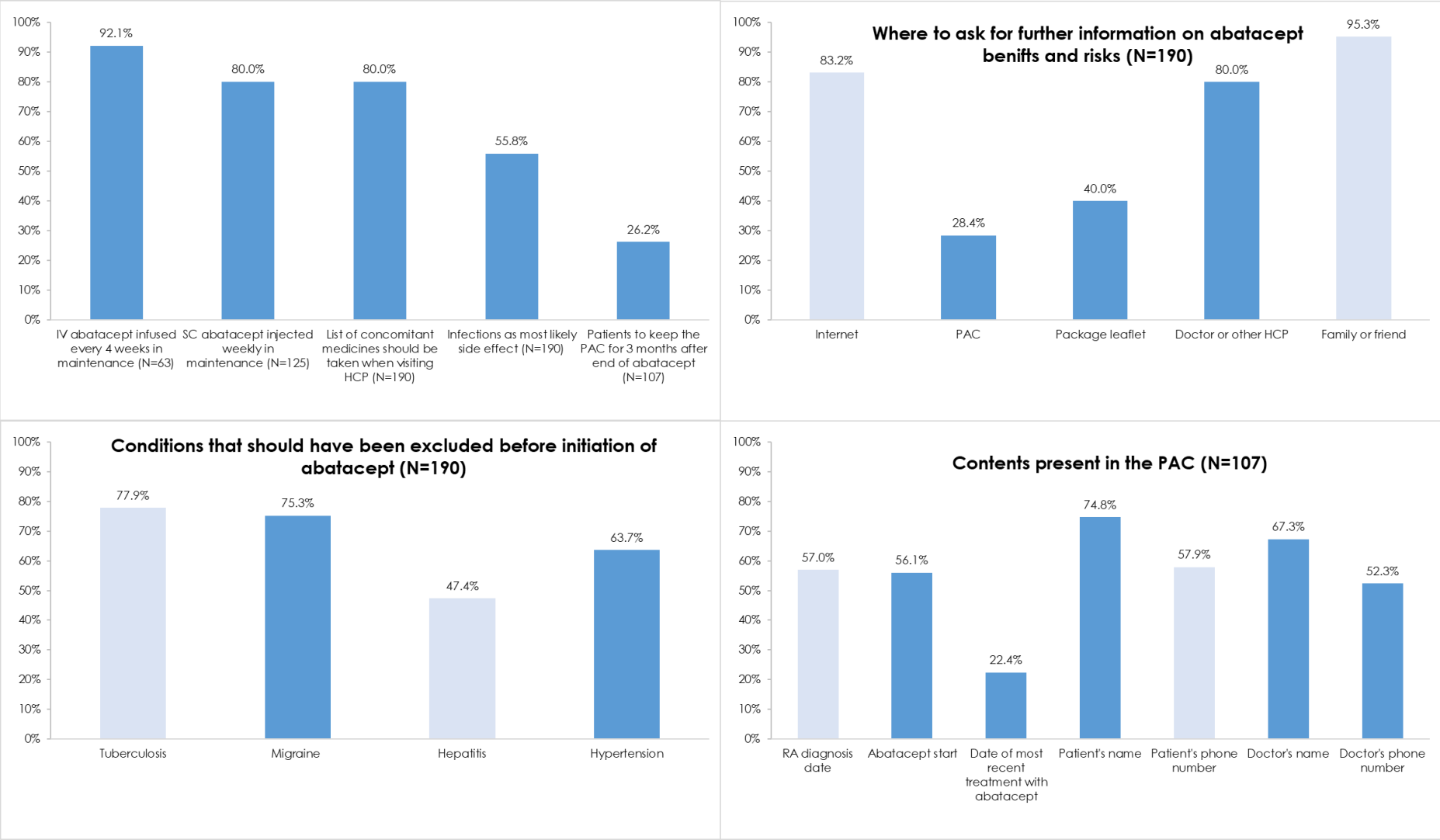


Figure 21. Percentage of correct knowledge in patient surveys. Positive correct responses (=Yes) are displayed in dark blue and negative correct responses (=No) in light blue

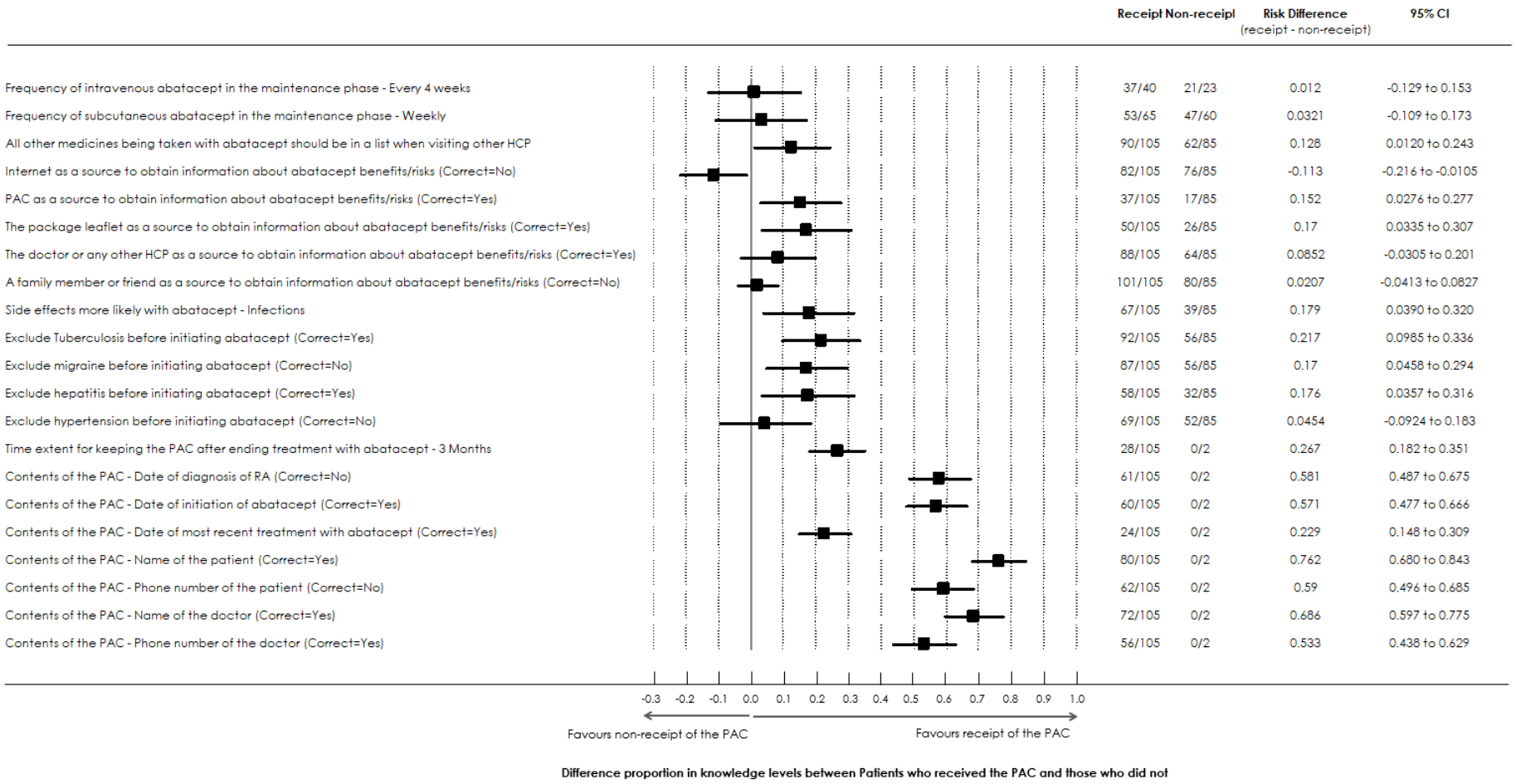


Figure 22. Proportion differences in level of correct knowledge in patient survey according to receipt/non-receipt of the PAC

The percentage of patients who were aware that a list of all other medicines being taken with abatacept should be carried at any visit to a HCP was higher among those who recalled having received the PAC than in those who did not (85.7% vs 72.9%; *p*=0.029). By contrast, the recommendation to keep the PAC for 3 months after the last dose of abatacept was only known by 26.2% of patients who received the PAC vs 0.0% of those who did not.

The majority of patients reported that HCPs informed them about the side effects of abatacept (66.1%; 125/189). Implementation of behaviour was also assessed through hypothetical scenarios of when to seek immediate medical attention: correct responses were 68.9% (131/190) for fever, 80.5% (153/190) for chest tightness, 66.3% (126/190) for wheezing and 64.2% (122/190) for severe dizziness or feeling light-headed.

The mean behaviour score was significantly higher among patients who recalled having received the PAC compared to those who did not (70.3% vs 64.2%; *p*=0.027).

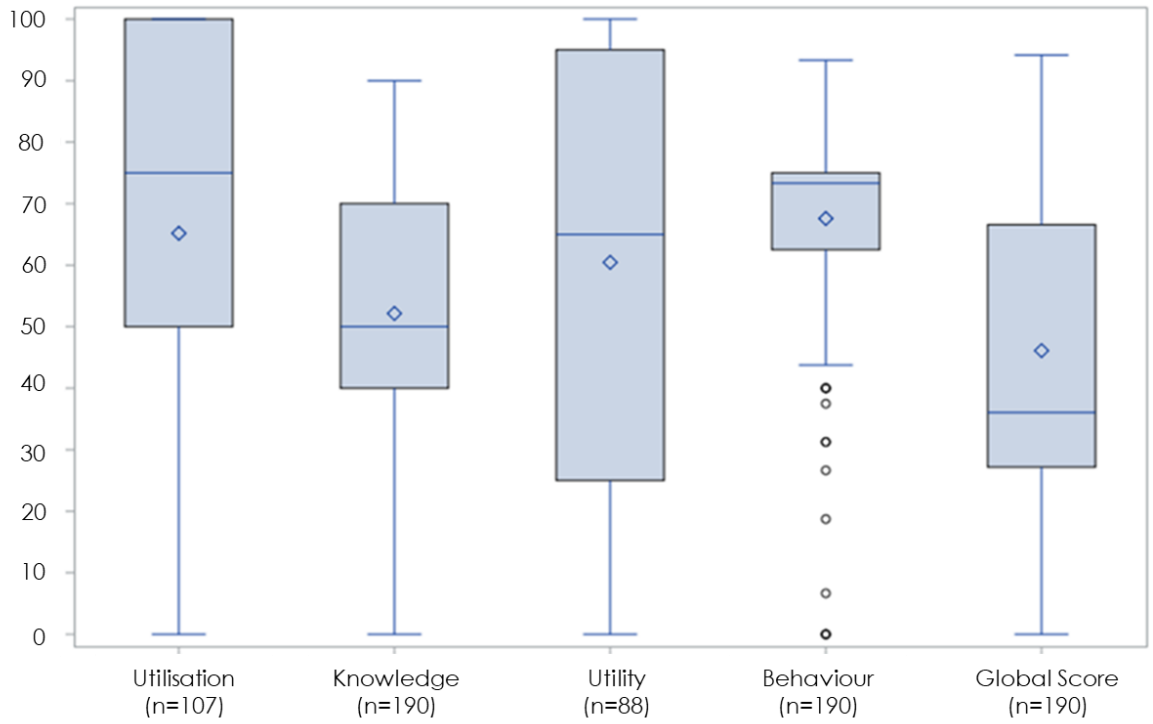


Figure 23. Scores in the patient survey: Utilisation, Knowledge, Utility, Behaviour and Global Score in the patient survey

The mean (SD) global score was 46.1% (23.1) overall and higher among patients who indicated having received the PAC than in those who did not (65.6% vs 26.9%; *p*<0.001).

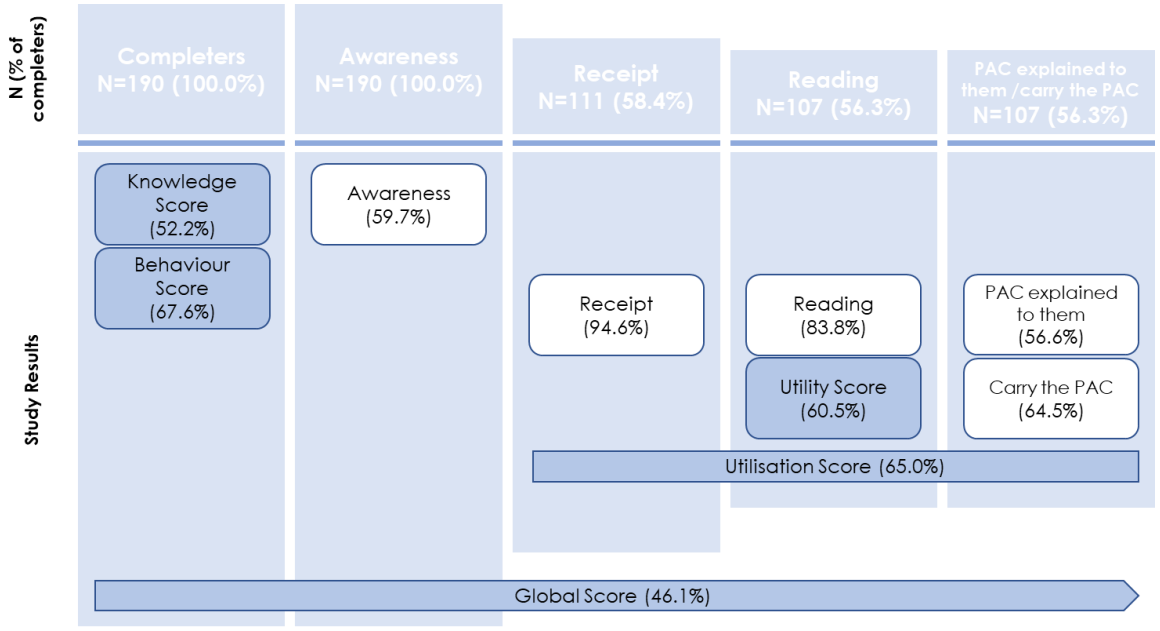


Figure 24. Summary of patient survey results

6.4.3. Retrospective Chart Review: Correlation of Patient Survey Process Indicators with Clinical/Safety Outcomes

Of the 190 patients who completed the patient questionnaire, 181 had outcomes data extracted. The nine patients without outcomes data were due mainly to closure of the study before the data could be collected. Pre-treatment screening tests for TB and for VH were available in 83.4% (151/181) and 69.1% (125/181) of patients, respectively; 76.8% (116/151) had the results available for TB and 88.8% (111/125) for VH before abatacept.

During the follow-up period, seven of 181 patients (3.9%) had infections leading to emergency room attendance and 11 (6.1%) had infections leading to hospitalisation. The mean (SD) time from symptom onset of the infection to receiving medical attention (per patient), in 16 patients with data available, was 6.8 (± 6.9) days.

Table 17. History of infections during the follow-up

Follow-up	Overall N=181
Time from first symptom onset of infection until receiving medical attention (days) (per patient average)	
n (n missing)	16 (165)
Mean (Standard Deviation)	6.8 (6.9)
Median (Q1-Q3)	4.0 (1.0 - 13.5)
Min - Max	0.0 - 21.0
Patients with infections leading to emergency room during the follow-up	
n (n missing)	181 (0)
n (%)	7 (3.87)

Follow-up	Overall N=181
Patients with infections leading to hospitalisation during the follow-up	
n (n missing)	181 (0)
n (%)	11 (6.08)

In the correlation analysis (Table 18), the percentage of patients with infections leading to hospitalisation increased as patient survey global scores decreased: scores of ≥67%, 34-67% and ≤33% were associated with hospitalisation rates of 2.5% (1/40), 5.2% (3/58) and 8.4% (7/83), respectively (p=0.44). A statistically significant association was observed for the correlation of the global composite score and screening for TB: global scores of ≥67%, 34-67% and ≤33% were associated with screening for TB scores of 60.0%, 81.0% and 54.2%, respectively (p=0.004). No significant correlation was found for screening for VH: global composite scores of ≥67%, 34-67% and ≤33% were associated with screening for VH scores of 57.5%, 70.7% and 56.6%, respectively. There was no correlation for emergency room visits and by days from first onset of symptoms of infection to receiving medical attention with global scores.

Table 18. Correlation Analysis

		Global Score (from patient survey)										
		High (>67%)			Medium (34%-67%)			Low (≤ 33%)				
Categorical variables	**Valid n**	**n**	**% col**		**n**	**% col**		**n**	**% col**		**Test**	**p-value[b]**
Patients with results of any pre-screening test for TB before Abatacept												
Yes	116	24	60.00		47	81.03		45	54.22		Chi-square test	**0.004** [b]
No	65	16	40.00		11	18.97		38	45.78			
Patients with results of any pre-screening test for viral hepatitis before Abatacept												
Yes	111	23	57.50		41	70.69		47	56.63		Chi-square test	0.206
No	70	17	42.50		17	29.31		36	43.37			
Patients with infections leading to unplanned hospitalisation during the follow-up												
Yes	11	1	2.50		3	5.17		7	8.43		Fisher exact test	0.440
No	170	39	97.50		55	94.83		76	91.57			
Patients with infections leading to emergency room visit during the follow-up												
Yes	7	1	2.50		2	3.45		4	4.82		Fisher exact test	1.000
No	174	39	97.50		56	96.55		79	95.18			
Continuous variables	**Valid n**	**n**	**Mean**	**Std. Error**	**n**	**Mean**	**Std. Error**	**n**	**Mean**	**Std. Error**	**Test**	**Statistic**	**Value**	**p-value**
Number of days from first symptom onset of infection until receiving medical attention (average per patient) [a]	16	3	7.0	3.464	5	3.6	2.619	8	8.8	2.725	Mann-Whitney	U	8.50	0.103

a. The univariate analysis was performed among groups with at least 5 cases.

b. Bold values correspond to statistical significance of the differences between groups (p<0.05)

c. *Yes* is associated with "*Medium Level*" and *No* with "*Low Level*"

6.4.4. Healthcare Professional Survey

The disposition of HCPs in the study is presented in Figure 25. Only 320 HCPs were evaluable among 2385 HCPs invited to participate. From these 320 HCPs, only 107 were eligible and 79 (50 physicians and 29 nurses) completed the questionnaire. The percentage of completers/invited was 3.3% (79/2385) and that of completers/eligible was 73.8% (79/107).

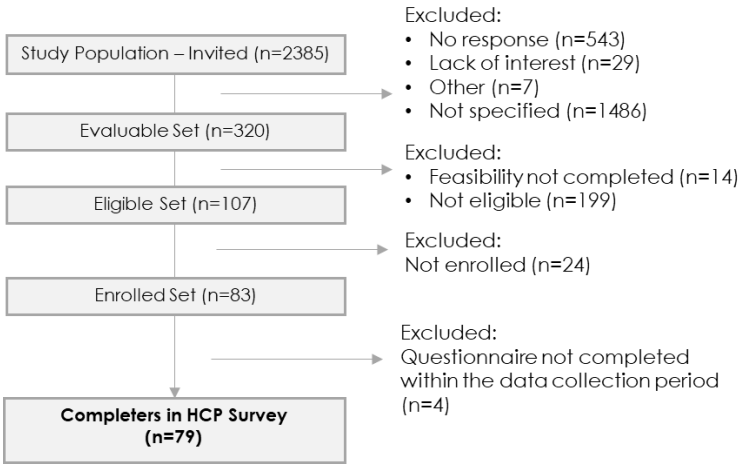


Figure 25. Study Population in HCP Survey – Objective 4

6.4.4.1. Healthcare Professional Characteristics

The distribution of participants among the participating countries was: 29.1% (23/79) in France, 26.6% (21/79) in the UK, 21.5% (17/79) in Spain, 17.7% (14/79) in Germany and 5.1% (4/79) in Sweden.

The characteristics of patients in the survey are summarised in Table 19. HCPs were mainly aged between 36 and 55 years (38.0% 36-45 years; 35.4% 46-55 years). Most respondents were female (63.3%, 50/79) and physicians (63.3%, 50/79). Almost half (45.57%, 39/79) had 11-20 years of experience. The mean (SD) number of RA patients managed personally with Abatacept in the previous 12 months was 29.3 (62.6). The main roles of HCPs in the treatment of patients with Abatacept were: follow-up (89.9%, 71/79), discussion of the use of Abatacept (76.0%, 60/79) and discussion of the benefits of Abatacept (73.4%, 58/79). Eight (10.1%) HCPs had participated in clinical trials with Abatacept in the previous 12 months. The majority belonged to academic centres (60.3%, 47/78) with a median of 21.0 (95% CI: 13.0-42.0) patients treated with Abatacept in the previous year. Most centres had specialist nurses in their departments (86.8%, 66/79).

Table 19. Healthcare Professional Characteristics

		HCPs N=79
Country		
France	n (%)	23 (29.11)
Germany	n (%)	14 (17.72)
Spain	n (%)	17 (21.52)

		HCPs N=79
UK	n (%)	21 (26.58)
Sweden	n (%)	4 (5.06)
Age group		
18-25 years	n (%)	0 (0.00)
26-35 years	n (%)	10 (12.66)
36-45 years	n (%)	30 (37.97)
46-55 years	n (%)	28 (35.44)
56-65 years	n (%)	11 (13.92)
> 65 years	n (%)	0 (0.00)
Gender		
Male	n (%)	29 (36.71)
Female	n (%)	50 (63.29)
Type of HCP		
Rheumatologist	n (%)	49 (62.03)
Rheumatologist in training	n (%)	1 (1.27)
Specialist nurse	n (%)	29 (36.71)
Internist	n (%)	0 (0.00)
Years managing RA patients		
< 5 years	n (%)	3 (3.80)
5 - 10 years	n (%)	19 (24.05)
11 - 20 years	n (%)	36 (45.57)
> 20 years	n (%)	21 (26.58)
Number of RA patients managed personally with Abatacept in previous 12 months		
	n (n missing)	79 (0)
	Mean (Standard Deviation)	29.3 (62.6)
	Median (Q1-Q3)	12.0 (6.0 - 24.0)
	Min - Max	2.0 - 400.0

6.4.4.2. Healthcare Professional Survey Results

The majority of HCPs (89.7%; 70/78) were aware of the PAC, of whom 68.0% (53/78) reported having had access or receiving it. Half of those who had received the PAC offered it to patients with the first prescription (50.0%; 19/38) and 47.4% (18/38) did at or before first administration. The PAC was mainly provided by nurses (66.7%; 52/78). Among HCPs who received or had access to the PAC, 71.7% (38/53) also read it. Most HCPs explained the content of the PAC to their patients at least sometimes (65.8%; 25/38). More nurses than physicians were aware (93.1% vs 87.8%), had accessed (77.8% vs 74.4%), read (90.5% vs 59.4%), distributed (80.9% vs 65.6%) and explained the content (94.1% vs 42.9%) of the PAC.

Among readers of the PAC, the mean (SD) utilization score was 50.9% (37.3). The level of helpfulness of the PAC was 70.4% (20.0), clarity 75.0% (25.3), conciseness 73.7% (23.2), completeness 71.1% (25.0) and brevity 66.4% (25.5), resulting in an overall mean utility score of 71.3% (20.4). A graphical representation of the scores is provided in Figure 26.

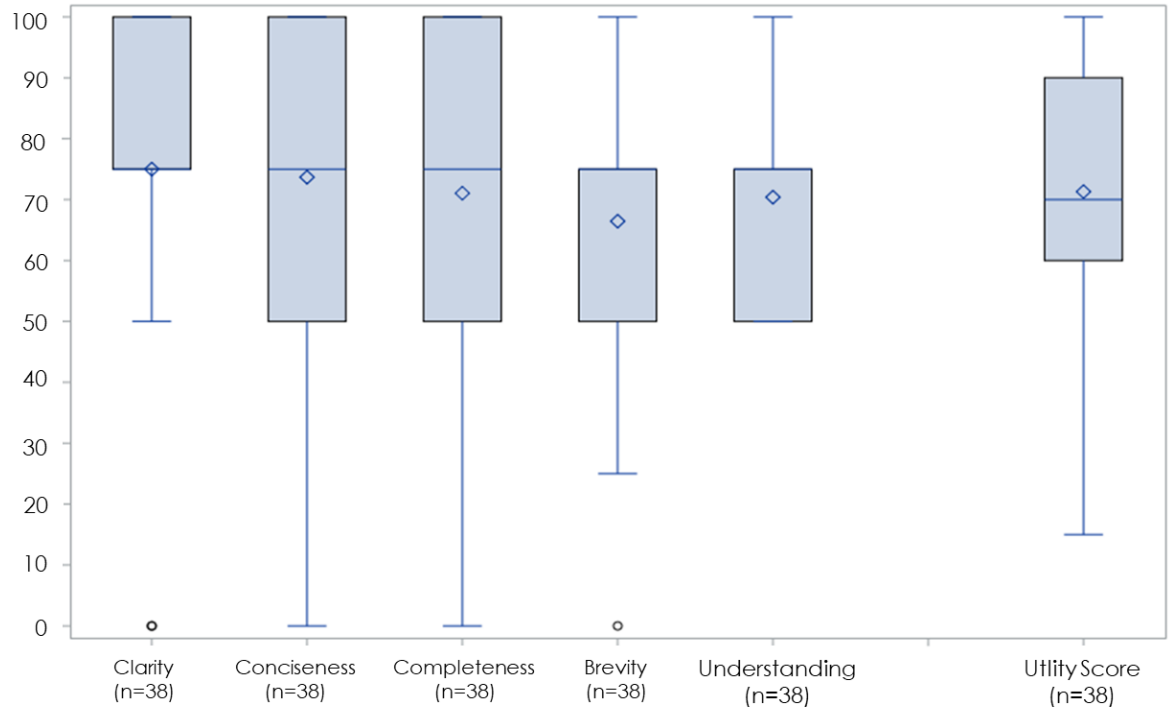


Figure 26. Clarity, conciseness, completeness, brevity, and understandability of the PAC in the HCP survey

Knowledge about the risk of infections was 84.8% (67/79) (Figure 27). The recommendations of pre-screening for TB and VH were known by 84.8% and 73.4% of HCPs, respectively. Figure 28 shows the differences in knowledge levels between HCPs who received the PAC vs. those who not. No statistically significant differences in knowledge of any safety concerns were found between HCPs who did and did not receive the PAC. The mean (SD) knowledge score was 72.3% (17.0), and non-statistically significantly higher among those who remembered receiving the PAC compared to those who did not (74.8% vs 67.2%; *p*=0.274).

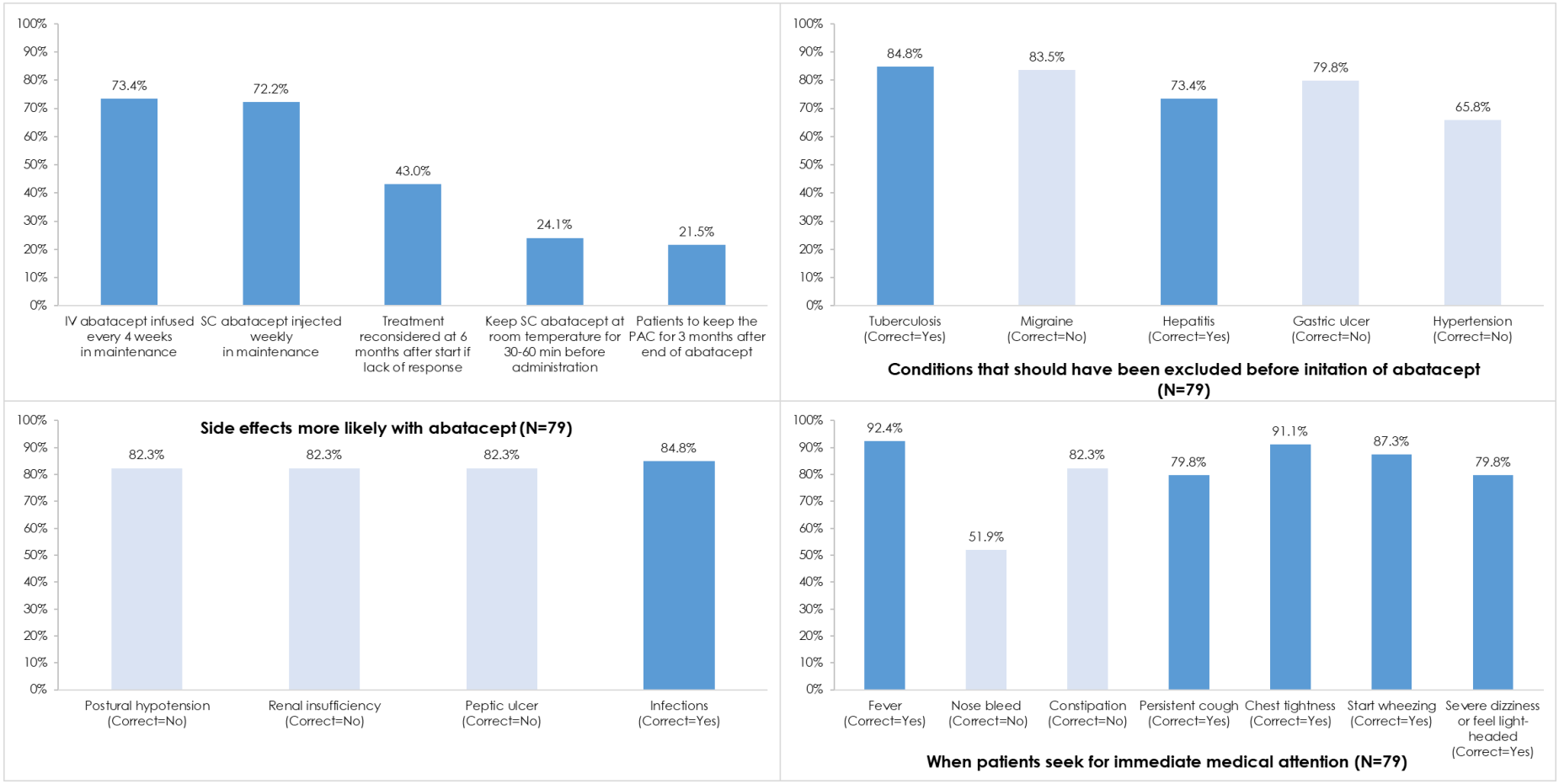


Figure 27. Percentage of correct knowledge in HCP survey. Positive correct responses (=Yes) are displayed in dark blue and negative correct responses (=No) in light blue

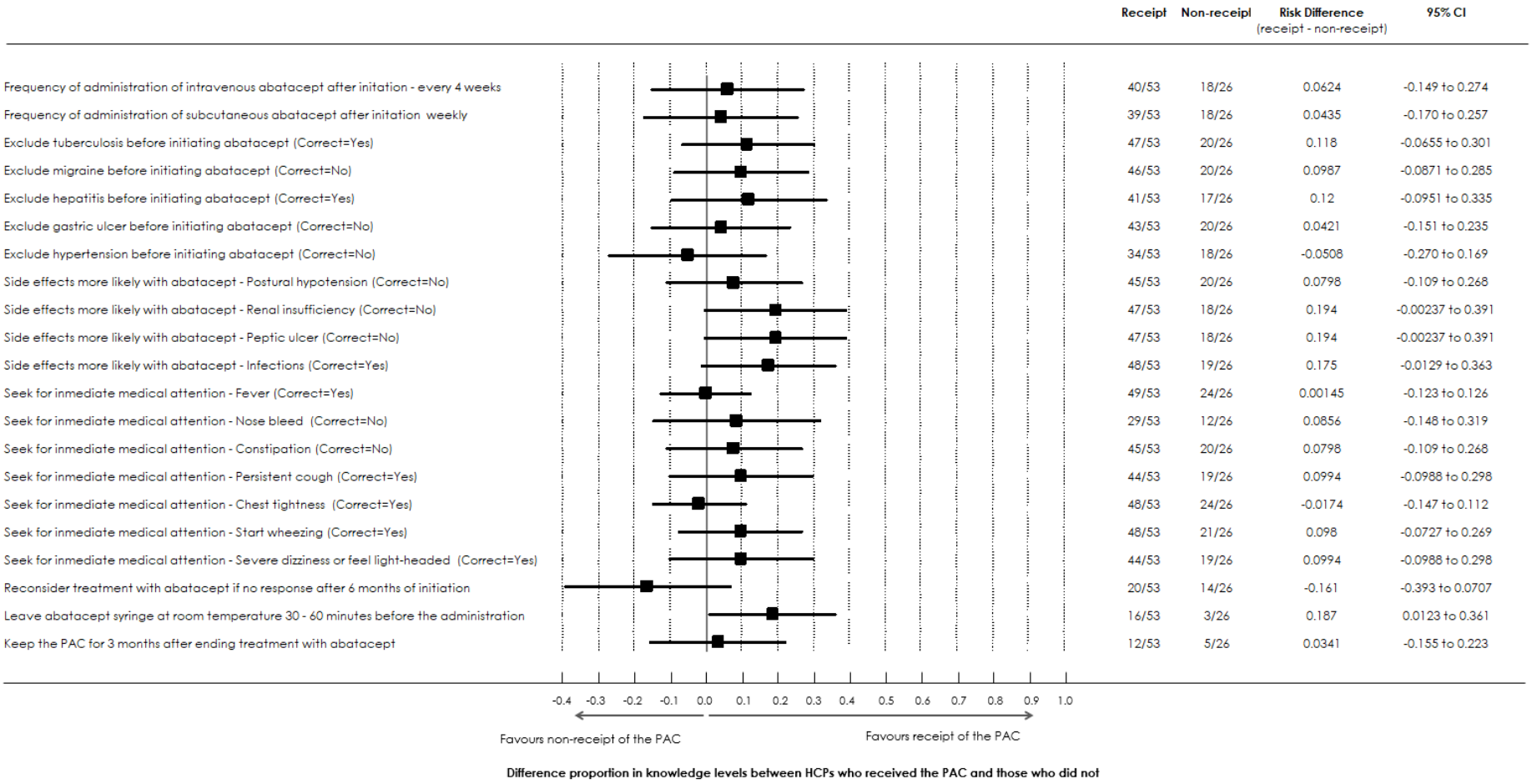


Figure 28. Proportion differences in level of correct knowledge in HCP survey according to receipt/non-receipt of the PAC

Most HCPs (96.2%) informed patients about the side effects of abatacept. The mean behaviour score was higher among HCPs who recalled having received the PAC compared to those who did not (79.2% vs 63.5%; *p*=0.027).

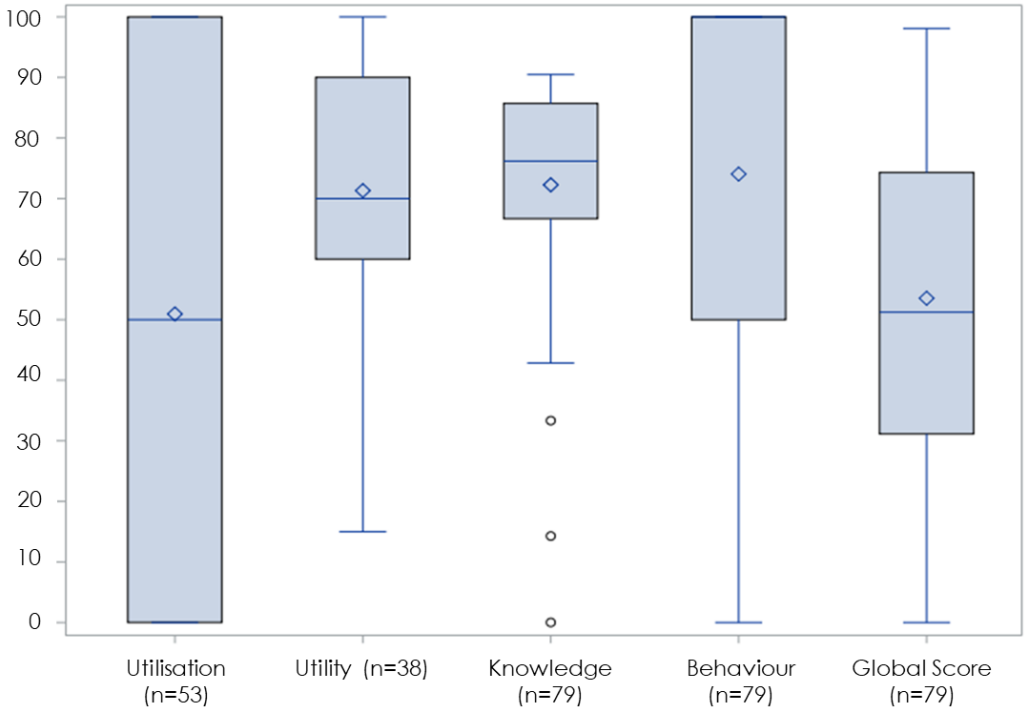


Figure 29. Scores in the patient survey: Utilisation, Knowledge, Utility, Behaviour and Global Score in the HCP survey

The mean global score was higher among HCPs who reported having received the PAC compared to those who did not (68.8% vs 33.1%; *p*<0.001).

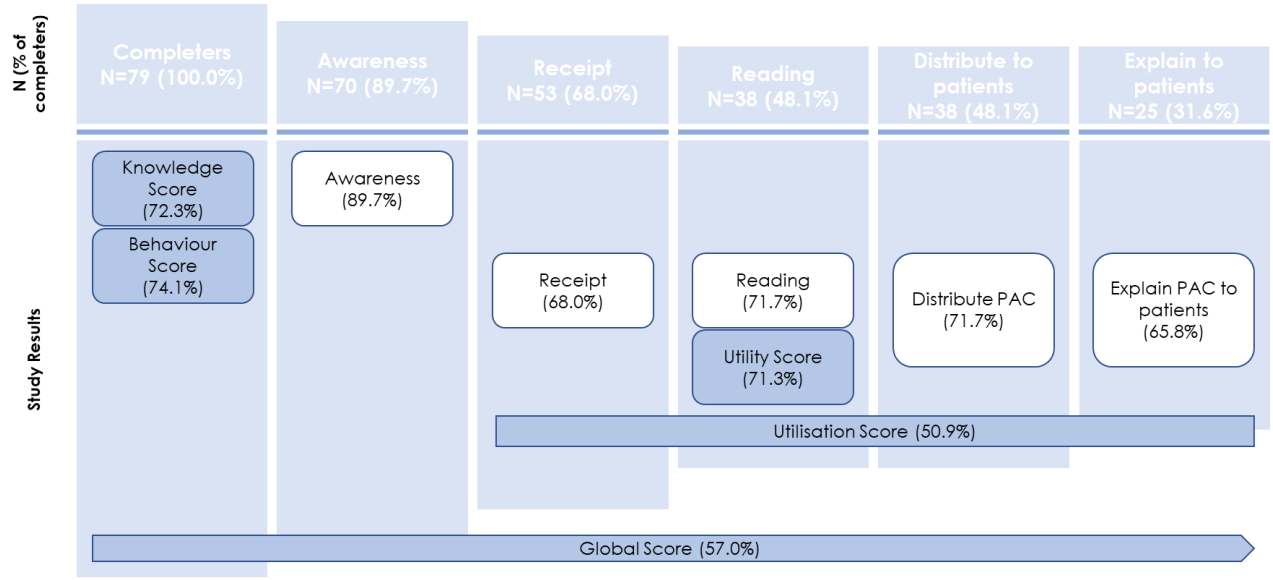


Figure 30. Summary of HCP survey results

7. Discussion

Risk minimisation evaluations may consist of measures of effectiveness evaluated at multiple levels with varying epidemiological designs and methodological approaches applied to accomplish the prespecified objectives. While previous research in the field looked at studies individually or reviewed studies descriptively, this thesis analyses subject participation, results and consequences of process indicators in EU RM Surveys, comprehensively evaluates RMEv using process indicators and outcomes beyond individual studies and provides a potential methodological framework for RMEv linking process indicators with outcomes at the patient level via a case example with results endorsed by EMA.

Process indicators are one component of RMEv which inform about the overall performance of the aRMMs; implementation of the aRMMs (receipt i.e., whether they reached the target population) and their use, as well as the level of understanding and behaviour implementation around key safety messages. Process indicators were assessed via EU RM Surveys in the studies reviewed in this thesis, which are becoming a standard tool in this research field. As such, survey studies allowed for pooling of results across studies and combined interpretation, however, there was great variability in the way study participation data and results were presented and defined across reports and publications, which may benefit from further standardization.

Low participation rates in surveys may result in selection bias, and results which are not generalizable. Participation rates may be defined and calculated in various ways. The pooled completers/invited rates found in Manuscript I reflect the difficulties encountered in attaining participation in HCP surveys, with an average of 1000 HCPs needed to be invited to recruit a sample of about 50 HCPs. Despite recruitment efforts and changes in planned strategies (e.g., extension of the data collection period, adding new countries and/or sites, remove random selection and a mixture of contingencies), pre-defined sample sizes were only reached in half of the included HCP surveys. Low response rates and lack of generalizable results were also highlighted by regulators in the assessment reports of at least half of the studies as a major limitation to interpret results and make appropriate decisions. In other studies, this was considered 'acceptable' owing to the rarity of the disease with a limited number of HCPs available for recruitment and restricted to very specialized settings or to low usage or slow penetration of the product. In patient/caregiver surveys, participation data were difficult to interpret due to the small number of reports available, and if available the small sample sizes and limited information on selection methods and number of patients invited or eligible in the study reports. More than half the studies failed to meet their pre-specified sample sizes, which may be due to low usage of specialty drugs, patients with grave conditions not being in a condition to complete a questionnaire, lack of interest by participating sites that prioritize other studies and low fees paid for these studies. Abstract II also found low participation in surveys, especially for patient surveys. The ISPE

Whitepaper highlights the importance of compensation fees according to fair market value standard in each country as a way to secure recruitment [60] and potentially increase representativeness [101]. However, it is acknowledged that incentives are still low compared to other competing studies such as clinical trials. HCPs also consider surveys of low scientific value. These are potential reasons that may contribute to low participation rates.

The evaluation of aRMMs via surveys is on top of a background of varying clinical practice and guidelines for prescribing and monitoring which are variably followed in different EU countries. Thus, a range of countries is usually included in these studies, some countries being overrepresented. Abstract II reported an average of 6 participating countries with a maximum of 18 in HCP surveys, and 5 with a maximum of 10 in patient surveys, being the UK, Spain, France and Germany the most frequently included countries and the highest recruiting. However, conclusions are difficult to derive about the country variation of results. Heterogeneity of studies by design, characteristics of participants, clinical situations of use, results, with the limited number of studies available may limit generalizability but provide an overall summary of the current situation.

Strategies to minimise selection bias remain under discussion. Recent initiatives aim to establish a conceptual framework to inform engagement interventions of patients and HCPs in the context of regulatory pharmacovigilance [14]. In this respect, the recent update of the ENCePP Methods guide [102] states: 'The increasing use of online RMM require that survey methods adapt but should not sacrifice representativeness by accessing only populations which visit these websites and should provide evidence that the results using these sampling methods are not biased. Similarly, the increasing use of HCP and patient panels needs to ensure that survey methods do not sacrifice representativeness by accessing only self-selected participants in these panels and should provide evidence that the results are not biased by using these convenient sampling frames.'

Receipt of aRMMs (sometimes referred to as distribution or awareness) is one of the process indictors most frequently assessed in surveys (70% of HCP surveys and 100% of patient surveys; Manuscript I). Manuscript I and II show that receipt was not recalled by over 40% of respondents, varying somewhat with the type of materials. According to regulatory assessment reports, a third of the studies with ARs available required reinforcement of distribution strategies for existing aRMMs in all or some study countries or re-distribution and re-evaluation of their effectiveness. In recent years developments have been directed towards the implementation of digital materials by MAHs to make aRMMs easily accessible on their websites and monitor access in a real-time manner, and by local agencies making materials available through regulatory websites, as well as to integrate materials into electronic prescribing systems [103], with a number of alert systems in place. Therefore, receipt may be expected to improve as digitalisation of materials increases.

Overall, if aRMMs are received, they are highly likely to be read and used, varying with the type of measure. Results in Manuscript II suggest that aRMMs impact the level of knowledge of patients to a lesser extent than they do among HCPs. This is not unexpected, as HCPs are more knowledgeable in health-related matters and receive information from other sources (e.g., congresses, routine materials, company representatives, protocols in hospital departments). Reasons for the apparent lack of knowledge of key safety concerns in the materials among patients may include selection and educational level of patients, knowledge arising from several sources, reliance on caregivers, and the degree of contact patients have with their HCPs.

Self-reported data on the implementation of actions and behaviours, among patients and HCPs, were not analysable in Manuscript I due to the heterogeneity in the formulation of survey questions/responses and presentation of reported results. This suggests further standardization may be needed in the formulation, assessment, and reporting of these behavioural measures while allowing flexibility for the particular needs of individual products and disease settings. In Manuscript II, the implementation of behaviours among HCPs was comparable to the level of knowledge while it was higher than knowledge among patients.

It is argued that the analysis of knowledge and/or behaviour by receipt or use of materials is the strongest evidence that can be derived from surveys on whether materials truly have an effect, beyond a pure description of results. Knowledge was generally better among HCPs who had received, used or read the materials versus those who had not (Manuscript II). These results are encouraging as conjunctively show that aRMMs do have an effect on knowledge and behaviour. However, this analysis is not always included in surveys [79,83].

Results of process indicators observed in studies may be the consequence of the interplay of several factors, some resulting from the selection, quality, and implementation of aRMMs, and some from the study planning, design and methodology. In particular, the selection of the type of material and its design is an important aspect to consider. Manuscript I showed that overall, among patients, patient brochures, leaflets and guides are more frequently received, read and used than patient cards. Among HCPs, most respondents reported distributing or explaining the contents of both the patient cards and patient brochure to patients, with patient checklists and DHPCs being the lowest on receipt. However, the number of studies per material is small and thus further research is warranted to better understand the difference in process indicators between materials. Some recent publications point out the need to improve the quality of information provided in materials for these to be applicable in clinical practice e.g. in DHPCs [104]. In particular, general practitioners seem to perceive DHPCs to be commercially biased, discouraging reading [105].

The use of pre-specified thresholds for success (i.e., the extent to which the aRMMs achieved goals or target performance) in surveys is another aspect of substantial controversy. In Manuscript I almost a

third of the studies reported using a cut-off point to determine success, mostly for knowledge and behaviour varying in the level of success (e.g., majority, 70%, 80%). Similar findings were observed in previous reviews, where a minority of studies included success thresholds [45,51]. Existing guidelines in Europe do not require for a threshold to be pre-specified to guide results interpretation [2] however, this is sometimes requested by regulators. The use of thresholds may not always be actionable or sufficient on its own to guide interpretation of results [60]. Therefore, a case-by-case approach may need to be considered when deciding on the need for thresholds.

Other biases may be present in surveys, which include recall bias inherent in questions asking about the past, referral to materials as they complete the survey as well as the so called 'Hawthorne effect' which may lead to participants modifying their responses/behaviour as a consequence of the participation in the study. However, the latter may as well result in a positive bias towards the occurrence of outcomes, as a consequence of the increased awareness of the materials and safety concerns covered by the materials and questionnaire.

No prior research connected individual studies with regulatory consequences. Regulatory ARs in Manuscript I revealed that no changes to the materials or their implementation were recommended in 41% of studies based on results. The remaining sixty percent of studies required further action for distribution strategies, re-distribution, and follow-up assessment, changes to existing materials, further data awaited and, in a minority, removal of the materials. Inconclusive results requiring further data or discussion were reported in 18% of assessment reports. This suggests that in most cases results from EU RM Surveys provided data to inform regulatory decision making in relation to the existing aRMMs. However, there were instances where further evaluation or data from other studies were needed to reach a decision.

Some challenges remain in the design (partly inherent to their cross-sectional nature), conduct and reporting of these studies, which may benefit from more detailed guidance, use of common definitions, standardization of reporting and adding other study designs. This may facilitate the evaluation, interpretation, and comparison of results across studies.

Process indicators alone only provide a partial picture of the effectiveness of aRMMs and actions taken by regulators. GVP Module XVI and related publications [41] recommend that comprehensive approaches involving both process and outcome components be considered, and only when this is not clearly feasible, the effectiveness evaluation be based exclusively on process indicators [27]. The Report of CIOMS IX Working Group provides a practical framework for the conduct of such evaluations [17].

While recent reviews described RM studies overall [24,25,29,30], they did not comprehensively look into the combined evaluation of process indicators and outcomes. The use of the concept 'RMEv' in this thesis allowed for the combined interpretation of studies conducted for the same product.

Manuscript II showed that 18% of RMEv in Europe included outcomes in addition to process indicators. Additionally, of the 18 RMEv included in Manuscript II, direct measurement of health outcomes occurred in half of them, and only three assessed the effectiveness of aRMMs at the three evaluation levels: process indicators, behavioural outcomes, and health/safety outcomes. These would theoretically constitute the most complete RMEv programmes where the impact of the aRMMs can be fully assessed; whether they are being received and used by the target populations, with the assessment of the implementation of changes in clinical practice and its resulting effect on the occurrence of the outcome of interest. Therefore, more comprehensive approaches of this type, where possible, are encouraged.

The small proportion of RMEv with process indicators and outcomes found in Manuscript II may be due to limitations in finding appropriate data sources to quantify the outcome of interest (e.g. healthcare databases) [106–109], the use of valid methodological approaches to link the effect of the aRMM with the outcome or the feasibility of a study if the outcome is rare. Additionally, the choice of outcome measure (prescribing behaviour vs safety outcomes) needs to be consistent and proportionate to the safety concerns targeted by the aRMMs. All these underlying factors, which are generally discussed during the study design phase by the MAH and the competent regulatory authority, may have contributed to or dictated the choice of the final study approach (e.g., whether only process indicators or only outcomes are assessed). Despite these being broadly discussed in publications and relevant discussion forums; they remain unknown or incomplete at the individual study level and were therefore unavailable for assessment.

In most RMEv, outcome and process indicators were measured as part of the same study protocol. While surveys are becoming a standard tool to evaluate the effectiveness of aRMMs, a greater degree of variability and creativity is involved in the evaluation of outcomes, both in the design and the implementation of studies. In the other half, outcomes were assessed via indirect measures of drug utilisation or monitoring patterns, based on existing data. Where safety-related outcomes were measured, this was done via company safety databases (despite the well-known limitations of huge underreporting and that provide only aggregate national data), extraction from medical records or prospectively collected data. Outcomes may be influenced by many actions. Therefore, while the measurement of process indicators has limitations (e.g., cross-sectional assessment, self-reported, selection bias), they are needed to interpret whether the behavioural measures and outcomes were influenced by the aRMMs.

Manuscript II shows that studies evaluating process indicators and those evaluating outcomes within one RMEv were not always conducted in the same population/countries. In fact, correlation of process indicators with health/safety outcomes was attempted in very few studies; of the 18 RMEv, only in two the assessment of process indicators and outcomes was performed in the same patient population. Behavioural outcomes derived from utilisation studies were preferably evaluated in

countries or populations where feasibility of assessment is warranted by the availability of existing data sources. However, results may not always be generalizable to other countries where aRMMs are implemented. Regulatory frameworks, healthcare systems, prescription behaviour, monitoring requirements and drug utilisation patterns, may vary by country. This is observed in some studies where outcome results are substantially different across participating countries, limiting not only interpretation and decision-making but also extrapolation of findings to other regions. This variability is outlined by a recent review on studies evaluating DHPCs which highlights the need to identify nationally dependent factors and employ methods that better inform the effectiveness of drug risk communication at a regional level [49].

It is noteworthy that, in some cases, target safety concerns are related to events that do not primarily depend on patients taking action but require HCPs to behave according to recommendations (e.g. tests to screen for prior hepatic diseases [87] or for prior infections [84]). In these instances, risk communication and evaluation efforts should concentrate on HCPs. Other outcome measures relied on the assumption that, as patients become more knowledgeable about specific safety concerns, they will more readily identify relevant symptoms and signs, and therefore seek medical attention more promptly, minimising the consequences or the severity of the event [84,95]. Therefore, study assessments need to be tailored to the characteristics of the target safety concern.

The definition of an outcome indicator in this thesis includes intermediate measures related to behavioural changes such as off-label use or monitoring activities, as well as safety-related health outcomes. We aimed to differentiate between self-reported behaviour from patients or HCP from surveys, and prescribing behaviour based on actual clinical action data from medical records, which provide a higher level of evidence and may serve as indirect measures to assess the impact on health outcomes. Therefore, this thesis captures indirect measures of prescribing behaviour when direct measures of health/safety outcomes are not feasible or may not be necessary, as suggested by existing guidance [40].

Studies for the same active ingredient were considered as part of the same 'RMEv' for the purpose of Manuscript II, however, some studies were requested by different competent authorities, at different stages of the product lifecycle or with varying objectives. Even in the instance where studies may not have been originally planned together, we believe it is appropriate to group them with the same RMEv to allow for a combined interpretation of results. The selected study period (i.e. 2011 to 2019) was broad to identify as many studies as possible. However, some of these studies may have been initiated before the more stringent guidance on the evaluation of effectiveness of aRMMs (i.e. GVP Module XVI) came into effect in 2014. As a result, the quality of the conduct and reporting of the studies may have changed with time. It is also expected that as experience in the field grows, the standardisation and adherence to best practices will improve. Therefore, further research to investigate changes in the implementation of RMEv over time is warranted.

RMEv which only included behavioural and/or safety outcomes as well exist in the literature and are of great interest. Despite being identified in the review process (contributing to the number of EU RM studies in the selection process), they are not specifically covered by publications in this thesis. Some examples include diclofenac [110,111], codeine prescribing for children [112], strontium ranelate [113,114], flupirtine [115], mirabegron [116], pioglitazone [117,118], proton pump inhibitors [119], tigecycline [120], antipsychotics [121].

Studies conducted outside the EU (e.g. [122–124]) are also outside the scope of this thesis. One example worth highlighting is the study to assess the effectiveness of aRMMs in place for fentanyl buccal tablets, which consisted of a mixed-methods approach involving a knowledge and understanding survey, a retrospective prescription study, and web surveillance of illicit drug use [122]. Study approaches also have been identified which incorporate aRMMs into clinical trials to mitigate an identified safety concern [125,126], more of which may be found in the future.

Manuscripts I and II provide a screenshot of the status of EU RM studies at the time of the review. Therefore, EU RM studies recently published or registered in the EU PAS Register outside the review period would fall outside the scope of the research. Other studies may have had partial results available only, eventually becoming available in full. This the case of the studies evaluating the effectiveness of aRMMs for voriconazole and valproate. The FSRs were retrieved at the time of Manuscripts I and II while now also the manuscripts are available [127–131]. In the case of vismodegib, while only one manuscript was available at the time of Manuscript II, now a recent publication reporting the results of another EU RM Survey can be found in the literature [132].

Based on the findings of Manuscript II, while great efforts are being made to evaluate processes and outcomes where feasible, there remains room to increase studies that correlate processes and outcomes at an individual patient level to provide more comprehensive evaluation of the implementation of aRMMs and link outcomes to the use of materials, as requested by regulatory agencies. The availability of new sources of information (e.g., social medial [133]), may also provide additional opportunities for different forms of evaluation with novel designs.

The study reported in Manuscript III is one example of such approach, as it employed a hybrid design to evaluate the effectiveness of the abatacept PACs using both process indicators (via surveys) and clinical/safety outcomes (via retrospective chart review) in the same patients. This is the first published study of its type of which we are aware.

For the study reported in Manuscript III, patients were recruited via physicians and the lower than anticipated recruitment of patients appeared to be due to low use of abatacept in the study centres. In the HCP Survey, while the planned number of HCPs was recruited, it involved a significant recruitment effort requiring invitations to 2385 potential HCPs. How many of the 2029 non-responders, despite several reminders, were not eligible is unknown but we do know that some two thirds of all

responders were not eligible. Thus, the generalisability of the results has some uncertainty. Nonetheless, low response rates in surveys involving HCPs is a well-known limitation and has been previously acknowledged in other studies of this kind [25,82,83].

The range of countries with different healthcare systems and multiple sites in Manuscript III provides a global overall picture of the performance of the abatacept PACs among RA patients and HCPs in Europe.

Awareness of the PAC was moderate among patients. More reassuring is that if patients receive the PAC, they most often read it. Higher levels of correct knowledge about the risk of infections and pre-screening for TB and VH, behaviours around these messages and the global score were observed among patients who recalled having received the PAC compared to those who did not, which suggests that the PAC may have an effect on levels of knowledge and behaviour.

Potential response bias was minimised with ´best practice´ qualitative techniques to develop the questions and their implementation in the online survey such as sequencing of questions, skipping questions was not permitted, questions could not be changed once submitted. Survival bias may as well be present in this survey, as patients who had stopped treatment with abatacept for any reason before the three months' time window for inclusion were not eligible for the survey.

Despite low numbers of clinical and safety endpoints, a numerical increasing trend was observed in the primary endpoints of infections leading to hospitalisation and infections leading to emergency room visits as the patient survey global score decreased. However, these results are not statistically significant and would require a bigger sample for confirmation.

There is potential bias in extrapolating current understanding and implementation in patient surveys with past events in this retrospective study. The scores were created to assess the impact of the PAC in the target populations, including those who reported being aware and having received the PAC versus never having received the PAC.

Most HCPs reported being aware of the PAC, with fewer accessing and reading it. Nurses were identified as the HCP responsible for providing the PAC by more than two-thirds of HCP respondents. Thus, the importance of the role of the rheumatology nurse responsible for handling and explaining the content of the PAC to the patient is clear. Most HCPs considered the PAC to be clear, concise, complete, and helpful. Knowledge about the risk of infections was high among all HCPs, with no differences observed between HCPs who received the PAC and those who did not. HCPs who manage RA patients are familiar with biologic therapy – infection is a known common risk - and may acquire most of their information about the use and risks of abatacept from sources other than the PACs. Behaviour and global scores were higher among HCPs who had access to the PAC, suggesting a potential impact around implementation of some key messages.

While differences in results in those who receive and do not receive the PAC is the strongest evidence from the surveys alone, they may not be unconfounded comparisons. Thus, results need to be cautiously interpreted.

The practical impact of this study resulted in no modifications to the content of the PAC or further evaluations being requested by EMA regulators. Therefore, the results support the effectiveness of the abatacept PACs. The study results suggest that the distribution of the PAC to patients could be improved, despite already being included inside the abatacept product packaging and that nurses should be the main target of any strengthened distribution efforts, where feasible.

The main strength of this study was the ability to correlate survey responses with clinical and safety outcomes in the same patients. The study used a novel design that bridges the gap of linking process indicators with outcomes for the assessment of effectiveness of RMMs, strengthening the clinical relevance of results from surveys. Previous studies have been conducted to assess outcomes and process indicators [19,2], though no designs comprising within-person correlations have been reported in the published literature, as far as we are aware.

This study may provide a potential framework for the evaluation of aRMMs via process indicators, behavioural and health/safety outcomes. This framework may be applied in circumstances where the aRMMs are implemented at the time of drug approval (with no possibility of a pre-implementation period for evaluation), patients are the target of the aRMM efforts, the outcome of interest is not rare and can be obtained from medical records. However, the applicability of this approach to evaluate the effectiveness of RMM interventions for other products needs to be assessed on a case-by-case basis.

To conclude, it is apparent that great efforts are being made and substantial amount of research is being conducted in Europe, to advance the field of therapeutic RM and shed light into uncertainties surrounding the conduct of studies, with numerous research groups and initiatives representing regulatory, academics and industry driving it. Additionally, the EMA promotes transparency of post-market data and regulatory decision-making in Europe, for example, facilitating publication and information sharing of PASS via the EU PAS Register [4]. In this regard, one example of transparency and stakeholder engagement in the context of RM is the recently published analysis of patient and HCP input on valproate teratogenicity and its RMMs, which drew proposals to be considered by PRAC for piloting [134]. However, room remains for improvement of methodological approaches and conjunctive efforts. The paper by Arlett highlights the need for more robust analytical approaches to generate results that are valid and informative [14]. This article also invites relevant stakeholders to engage in discussions and participate in the consultation initiative that the EMA will launch in 2020 regarding methodological guidance on measuring the impact of PhV and RM [14].

8. Lessons Learned and Recommendations

Based on the findings of this thesis, some lessons learned, and recommendations can be drawn.

- **Standardisation of Assessment and Reporting of Process Indicators via EU RM Survey Studies:**

GVP XVI Annex 1 provides specific guidance on the methodology to be used in RM Survey Studies and several other documents and articles exist to guide these types of studies [2,40,60]. Previous reviews have described the methods and challenges used in studies evaluating the effectiveness of aRMMs [32,34,35,42,48,52,70]. Nevertheless, the results of this thesis illustrate the need for more detailed guidance, recommendations, and standardization to facilitate the design, conduct and reporting of these studies.

The need for detailed guidance about the conduct and reporting of survey studies is acknowledged in survey research [135]. Some publications attempt to provide best practices in conducting and reporting survey studies; however, they do not tackle specific aspects and challenges observed in EU RM Survey Studies [136]. Meaningful interpretation and comparison of study results requires the use of common definitions and standardization of reporting. Some studies did report response rate and others reported it variably.

Recommendations for standardization may include definition of response rates, pre-defined sample population, and a full description of the participant selection process using flowcharts and summary tables to display the number of subjects invited (includes those responding and not responding to invitations), subjects successfully contacted, subjects screened who respond to screening questions, eligible, those who complete the survey questionnaire (i.e. completers) and the number of subjects excluded with reasons. There is insufficient detail in some reports to assess how well the planned sampling methods performed. Therefore, reports should clearly indicate what was planned in the protocol and what was finally feasible. Reports should also describe efforts made to recruit the pre-specified sample size and emphasize the context of the evaluation, e.g., orphan indication. Guidance documents have used 'responded divided by the number of eligible subjects in the sample' as a definition of response rate [66], i.e. completers/eligible. Operational definitions and formulas for calculating response rates, cooperation rates, refusal rates, and contact rates in surveys as well as a description of available sampling methods are available and can serve as a basis for further standardization with a focus on risk minimization [137]. We propose the following minimum to be reported: completers/eligible, completers/invited and completers/targeted. This should ideally be provided overall but also by country so that country-level participation can be further assessed.

A variety of terms and definitions were used to describe process indicator dimensions. Standardization of the dimensions used in the RMMs may be useful to compare dimensions in different studies.

Proposed dimensions could be categorized into the following 4 categories: receipt of materials, use and reading, knowledge, and behavioural implementation. The inability to extract and analyse data on the implementation of behaviour resulting from aRMMs in these surveys needs attention as it is, arguably, the most relevant measure to assess the effectiveness of aRMMs in surveys.

Additionally, results of knowledge and behaviour should be presented and compared between those who receive and do not receive or used the materials as this is the strongest evidence from the surveys alone.

Strengthened recommendations to guide country selection and participation are also warranted e.g., minimum number of countries that should be included, reasons for selection, provision of country level participation data, how to extrapolate results to other countries not targeted in the evaluation.

- **Approaches that Combine Process Indicators with Behavioural and Health/Safety Outcomes:**

Drug utilization studies on prescribing behaviour or studies allowing for correlation of survey data with other patients descriptive or outcome data, whenever possible, may provide additional information and help overcome some of the limitations of cross-sectional study designs. Studies addressing prescribing behaviour or health/safety outcomes in Europe are reported in the literature. There are currently few designs correlating within-patient survey results (i.e., process indicators) with clinical and safety outcomes. These hybrid designs could help strengthen the validity of these survey studies. In the context of outcome evaluation, interpretation of the effectiveness of RMMs should take into consideration treatment adherence as this may have an impact on the occurrence of the safety event. This framework may be applied in circumstances where the aRMMs are implemented at the time of drug approval (with no possibility of a pre-implementation period for evaluation), patients are the target of the aRMM efforts, the outcome of interest is not rare and can be obtained from medical records. However, the applicability of this approach to evaluate the effectiveness of RMM interventions for other products needs to be assessed on a case-by-case basis.

9. Conclusions

The field of therapeutic RM has become an area of intensive research since the implementation of GVP XVI. As of October 2019, at least 129 EU RM studies had been designed and conducted to assess the effectiveness of RMMs for 102 different products in Europe. About forty percent of EU RM Surveys provided evidence that supports the effectiveness of RMMs based on regulatory Assessment Reports. The remaining sixty percent of studies required further action for distribution strategies, re-distribution, and follow-up assessment, changes to existing materials, further data awaited and, in a minority, removal of the materials. However, this review identified some challenges that remain in the design, conduct, and reporting of survey studies, which may benefit from more detailed guidance, use of common definitions, standardization of reporting. Some of the limitations of cross-sectional study designs (i.e., surveys) may be overcome by drug utilisation and outcomes evaluations which have been used conjunctively with EU RM Surveys in eighteen percent of RMEv to supplement the results of process indicators. There are currently few studies correlating within-patient survey results with heath/safety outcomes. This thesis provided a potential framework for the evaluation of effectiveness of aRMMs via a case study involving surveys and a retrospective chart review to correlate process indicators and safety outcomes in the same patients. This novel study design bridges the gap of linking process indicators with outcomes at the individual-patient level and strengthens the clinical relevance of results from surveys. The results support the effectiveness of the abatacept PACs. The practical impact of this study resulted in no modifications to the content of the PACs or further evaluations being requested by EMA regulators.

Great efforts are being made and substantial amount of research is being conducted in Europe, to advance the field of therapeutic RM and shed light into uncertainties surrounding the conduct of studies, with numerous research groups and initiatives involving regulators, academics and industry. However, room remains for improvement of methodological approaches and conjunctive efforts. The learnings of this thesis may be used by MAHs and regulatory authorities to inform the design of future RMEv approaches combining process indicators and outcomes.

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11. Conflicts of Interest

I was an employee of OXON Epidemiology at the time of conducting the review and meta-analysis of EU RM Surveys. This review was not funded.

I was an employee of OXON Epidemiology at the time of initiating the review of RMEv with process indicators and outcomes. This review was not funded.

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I am a current employee of Lilly Spain. However, none of this research was conducted as part of my work at Lilly; the work included in this thesis was initiated before I joined Lilly. Therefore, the opinions and discussions presented here are solely my own and do not express the views or opinions of my current employer.

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14. Supplementary Tables

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Table S1. List of Included Studies (Objective 1)

Study No.	Type of Drug	FSR Date	Data Collection Period	Type of RMM*	Timing of aRMMs*	No. of targeted safety concerns*	RMP Category[a]	Study requested by a regulator	Study design	No. countries		Type of Survey	Target population	Sample size		Process indicators with results[e]	Regulatory Submission	Regulatory Assessment Outcome
										N Target[d]	N Involved			N Target[d]	N Completers (% targeted)			
1[138]	Antifungal	17/05/2016	**6 months:** 02/09/2015 – 29/02/2016	Patient alert card, HCP Brochure/ Leaflet/ Guide, HCP Checklist	After drug approval, at extension of indication (prophylaxis)	3	PASS Cat 3	Commitment to the EMA	one-wave	10	10 (FR, DE, UK, IT, NL, HU, DK, IE, ES, AT)	HCP Survey	Specialists with drug experience	750	332 (44.3)	Receipt, use, reading, knowledge, behaviour	Submission of FSR to EMA/PRAC/ CHMP via a Type II Variation C.I.13, with changes to RMP	Changes to SmPC / Awaiting further results
2[71]	Antipsychotic	10/12/2013	**3.5 months:** 19/06/2013 - 27/09/2013	HCP Brochure/ Leaflet/ Guide, Patient Brochure/ Leaflet/ Guide	With new safety signal/ precautions	1	unknown	Netherlands	one-wave	8	8 (AT, DE, HU, IT, ES, RO, UK, SE)	HCP Survey	GPs, specialists with and w/o drug experience	800	800 (100.0)	Receipt, reading, behaviour	Unknown – AR not available	Unknown – AR not available
3[139]	Antithrombotic	12/02/2016	**7 months:** 12/02/2015 – 17/09/2015	Patient alert card, HCP Brochure/ Leaflet/ Guide	At extension of indication	1	unknown	EMA	one-wave	9	8 (UK, DE, ES, FR, DK, BG, CZ, SK)	HCP Survey	GPs, specialists with drug experience	400	411 (100.0)	Receipt, use, reading, knowledge	Submission of FSR to EMA/PRAC/CHMP via a Type II Variation C.I.13, with changes to RMP	Improve distribution of aRMM or re-distribute
												Patient/ Caregiver Survey	patients/caregivers	800	802 (100.0)	Awareness, receipt, reading, knowledge		
4[85]	Antiandrogen	20/04/2015	**11.5 months:** 14/02/2014 – 30/01/2015	DHPC, HCP Brochure/ Leaflet/ Guide	After new safety signal/ precautions	2	PASS Cat 3	EMA	one-wave	1	1 (DK)	HCP Survey	GPs with drug experience	25-75[b]	32 (100.0)	Knowledge	Type to Variation FSR to Danish Medicines Agency following EMA referral	No further action
5[140]	Antiepileptic	31/01/2014	**12.5 months:** 18/09/2012 – 04/10/2013	HCP Brochure/ Leaflet/ Guide	At product launch	2	PASS Cat 3	No	one-wave	8	8 (UK, DE, DK, ES, CH, SE, NO, SK)	HCP Survey	Specialists with and w/o drug experience	300	294 (98.0)	Reading, knowledge	Submission of FSR to EMA/PRAC/CHMP via a Type II Variation C.I.13, with changes to RMP	Changes to aRMM / awaiting further results / Follow-up Survey
												Patient/ Caregiver Survey	patients/caregivers	Not reported due to low recruitment				
6[141]	Antiepileptic	26/08/2015	**4 months:** 24/09/2014 - 30/01/2015	Patient alert card	After label changes/ restriction indication/ new safety signal	2	PASS Cat 3	No	one-wave	7	7 (BE, UK, ES, CH, NO, SK and China)	HCP Survey	Specialists with and w/o drug experience	400	414 (100.0)	Receipt, knowledge	Submission of FSR to EMA/PRAC/CHMP via a Type II Variation C.I.13, with changes to RMP	No further action
7[142]	Psychostimulant for ADHD and nootropics	20/11/2014	**3 months:** 30/06/2014 – 30/09/2014	HCP Brochure/ Leaflet/ Guide	At extension of indication	2	unknown	EMA	one-wave	5	5 (DK, NL, ES, SE, UK)	HCP Survey	Specialists with drug experience	250	250 (100.0)	Use, knowledge, behaviour	Submission of FSR to EMA/PRAC/CHMP via PSUSA procedure and update of RMP with summary results via a Type II Variation C.I.11.z	No further action
8[143]	Psychostimulant for ADHD and nootropics	27/03/2014	Wave 1 unknown Wave 2 **2 months:** 16/09/2013 - 22/11/2013	DHPC, HCP Brochure/ Leaflet/ Guide	After label changes/ new safety signal	2	unknown	No	multi-wave	5	5 (DK, NL, ES, SE, UK)	HCP Survey	GPs, specialists with drug experience	Wave 1: 550 Wave 2: 750	550 (100.0) unknown	Use, knowledge, behaviour		No further action
9[144]	Direct acting antiviral	16/10/2014	**2 months:** 13/01/2014 - 18/03/2014	Routine RMM	NA	1	unknown	EMA	one-wave	9	9 (AT, BE, DK, FR, DE, NO, SE, NL, UK)	HCP Survey	GPs, specialists, nurses, pharmacist with drug experience	289	323 (100.0)	Knowledge	Submission of FSR to EMA/PRAC via a Type II Variation C.I.13 to fulfil a PAM MEA	No further action
10[145]	Drug affecting bone structure and mineralisation	10/09/2015	Round 1 **5.5 months:** 01/01/2013 - 12/06/2013 Round 2 **8.5 months:** 28/08/2013 - 15/05/2014	Routine RMM	NA	1	unknown	No	multi-wave	9	9 (FI, FR, DE, IT, NO, ES, SE, UK)	HCP Survey	Specialists with drug experience	420	420 (100.0)	Knowledge	Submission of FSR to EMA/PRAC as part of PSUR & RMP update	aRMM implemented
11[146]	Antimalarial	26/06/2015	12-month survey **7 months:** 09/2013 - 03/2014 24-month survey **5 months:** 11/2014 - 03/2015	HCP Brochure/ Leaflet/ Guide	At product launch	4	unknown	EMA	multi-wave	5	3 (FR, DE, IT)	HCP Survey	GPs, specialists, pharmacist, with and w/o drug experience	180	77 (42.8)	Receipt, knowledge	Submission of FSR to PRAC/EMA/CHMP as part of PSUR procedure to fulfil a PAM LEG	Changes to aRMM / Improve distribution of aRMM or re-distribute / Follow-up survey
12[147]	Opioid	16/11/2016	**6.5 months:** 01/04/2015 - 15/10/2015	HCP Brochure/ Leaflet/ Guide	At product launch	5	unknown	EMA	one-wave	2	2 (FR, NL)	HCP Survey	GPs, specialists with and w/o drug experience	267	310 (100.0)	Receipt, use, knowledge	Submission of FSR to EMA/PRAC via a Type II Variation C.I.13, with changes to RMP	Improve distribution of aRMM or re-distribute / Awaiting further results or discussion

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Table S1. List of Included Studies (Objective 1)

Study No.	Type of Drug	FSR Date	Data Collection Period	Type of RMM*	Timing of aRMMs*	No. of targeted safety concerns*	RMP Category[a]	Study requested by a regulator	Study design	No. countries		Type of Survey	Target population	Sample size		Process indicators with results[e]	Regulatory Submission	Regulatory Assessment Outcome
										N Target[d]	N Involved			N Target[d]	N Completers (% targeted)			
13[78]	Antineoplastic agent	19/11/2015	**17 months:** 10/04/2014 - 11/09/2015	HCP Brochure/ Leaflet/ Guide, Patient Brochure/ Leaflet/ Guide	At product launch	6	unknown	EMA	one-wave	13	10 (AT, BE, FR, DE, IE, IT, ES, SE, NL, UK)	HCP Survey	Specialists, with drug experience	105-115[c]	94 (89.5)	Awareness, receipt, use, reading, knowledge, behaviour	Submission of FSR to EMA/PRAC via a Type II Variation C.I.13, with changes to RMP	Changes to aRMM
												Patient/ Caregiver Survey	patients/caregivers	28	28 (100.0)	Receipt, use, knowledge, behaviour		
14[148]	Antipsychotic	23/12/2016	Initial stage **12 months:** 27/07/2014 - 09/07/2015 Extension **5.5 months:** 10/07/2015 - 04/01/2016	HCP Brochure/ Leaflet/ Guide, Patient Brochure/ Leaflet/ Guide	At extension of indication	4	PASS Cat 2	EMA	one-wave	13	13 (AT, DE, DK, IE, IT, ES, SE, NO, UK, PT, SI, EL, CY)	HCP Survey	GPs, specialists, nurses, pharmacist with drug experience	150	118 (78.7)	Awareness, receipt, use, reading, knowledge, behaviour	Submission of FSR to EMA/PRAC via a Type II Variation C.I.13, with changes to RMP, to fulfil a PAM MEA	aRMM removed
												Patient/ Caregiver Survey	patients/caregivers,	148-158[c]	16 (10.8)	Awareness, receipt, reading, knowledge, behaviour		
15[75]	Antiandrogen	31/05/2016	**8 months:** 26/06/2015 - 21/02/2016	Patient alert card, DHPC, HCP Brochure/ Leaflet/ Guide	After label changes/ restriction indication/ new safety signal	1	PASS Cat 1	EMA	one-wave	5	5 (AU, CZ, FR, NL, ES)	HCP Survey	GPs, specialists with drug experience	500	759 (100.0)	Receipt, knowledge	Submission of FSR as a joint PASS to EMA/PRAC, not otherwise specified	Improve distribution of aRMM or re-distribute
16[149]	Antineoplastic agent	07/03/2017	**24 months:** 30/09/2014 - 30/09/2016	Patient alert card	At product launch	12	PASS Cat 3	EMA	one-wave	6	10 (AT, BE, DK, FR, DE, IE, IT, NL, SE, UK)	Patient/ Caregiver Survey	Patients/caregivers	25-40[b]	39 (100.0)	Awareness, receipt, use, reading, knowledge	Submission of FSR to EMA/PRAC/CHMP via a Type II Variation C.I.13, with changes to RMP	No further action
17[150]	Antineoplastic agent	07/03/2017	**24 months:** 30/09/2014 - 30/09/2016	HCP Brochure/ Leaflet/ Guide	At product launch	12	PASS Cat 3	EMA	one-wave	6	10 (AT, BE, DK, FR, DE, IE, IT, NL, SE, UK)	HCP Survey	Specialists with drug experience	150	98 (65.3)	Awareness, receipt, use, reading, knowledge	Submission of FSR to EMA/PRAC/CHMP via a Type II Variation C.I.13, with changes to RMP	aRMM removed
18[79]	Cardiac therapy	16/09/2015	**2 months:** 21/11/2014 - 15/01/2015	DHPC	At restriction of indication	1	unknown	EMA	one-wave	12	12 (BG, CZ, EE, FR, HU, LV, LT, PL, PT, RO, SK, ES)	HCP Survey	GPs, specialists with and w/o drug experience	1320	1123 (85.1)	Receipt, knowledge, behaviour	Submission of FSR as a joint PASS to EMA/PRAC, not otherwise specified	No further action
19[83]	Propulsive	13/06/2017	**3 months:** 04/01/2017 - 31/03/2017	DHPC	At product launch	1	PASS Cat 1	EMA	one-wave	5	5 (FR, DE, UK, BE. ES)	HCP Survey	GPs, specialists with drug experience	1880	1805 (96.0)	Receipt, knowledge	Unknown – AR not available	Unknown – AR not available
20[151]	Antidiabetic agent	29/03/2017	**6.5 months:** 16/05/2016 - 01/12/2016	DHPC, Patient Brochure/ Leaflet/ Guide	At new strength	1	PASS Cat 3	No	one-wave	3	3 (FR, DE, SE)	HCP Survey	GPs, specialists, nurses, pharmacist with and w/o drug experience	280	146 (52.1)	Awareness, receipt, use, reading, knowledge, behaviour	Submission of FSR to EMA/PRAC/CHMP via a Type II Variation C.I.13, with changes to RMP, to fulfil a PAM MEA	No further action
												Patient/ Caregiver Survey	patients/carers,	280	7 (2.5)	Not reported due to low recruitment		
21[152]	Antiviral	14/08/2017	**3.5 months:** 25/11/2016 - 07/03/2017	DHPC	After new safety signal / label changes	1	PASS Cat 3	No	one-wave	8	7 (BU, DK, FR, DE, HU, ES, UK)	HCP Survey	GPs, specialists, pharmacist with and w/o drug experience	200	301 (100.0)	Knowledge, behaviour	Submission of FSR to EMA/PRAC/CHMP via a Type II Variation C.I.13, with changes to RMP	No further action
22[84]	Immunosuppressant	29/09/2017	**6 months:** 11/2016 - 04/2017	Patient alert card	At product launch	6	PASS Cat 3	EMA	one-wave	5	5 (FR, DE, ES, SE, UK)	HCP Survey	specialists, nurses with drug experience	80	79 (98.8)	Awareness, receipt, use, reading, knowledge, behaviour	Submission of FSR to EMA/PRAC/ CHMPvia a Type II Variation C.I.13, with changes to RMP	Improve distribution of aRMM or re-distribute
												Patient/Caregiver Survey	patients/carers,	400	190 (47.5)	Awareness, receipt, use, reading, knowledge, behaviour		
23[85]	Antithrombotic agent	24/05/2017	**18 months:** 26/08/2015 - 26/02/2017	Patient alert card, HCP Brochure/ Leaflet/ Guide	At product launch	3	PASS Cat 3	EMA	one-wave	10	10 (AU, BE, DK, FR, DE, IT, NO, ES, SE, UK)	HCP Survey	GPs, specialists, nurses, pharmacists	384	370 (96.4)	Receipt, use, reading, knowledge, behaviour	Submission of FSR to EMA/PRAC/CHMP via a Type II	Improve distribution of aRMM or re-distribute

Table S1. List of Included Studies (Objective 1)

Study No.	Type of Drug	FSR Date	Data Collection Period	Type of RMM*	Timing of aRMMs*	No. of targeted safety concerns*	RMP Category[a]	Study requested by a regulator	Study design	No. countries		Type of Survey	Target population	Sample size		Process indicators with results[e]	Regulatory Submission	Regulatory Assessment Outcome
										N Target[d]	N Involved			N Target[d]	N Completers (% targeted)			
												Patient/ Caregiver Survey	Patients/carers	192	125 (65.1)	Awareness, receipt, use, reading, knowledge, behaviour	Variation C.I.13, with changes to RMP	
24[153]	Antimycotic for systemic use	30/05/2017	Wave 2 only **11 months:** 14/03/2016 - 13/02/2017	HCP Brochure/ Leaflet/ Guide	At product launch	5	unknown	EMA	multi-wave	8	8 (CZ, FR, DE, EL, IT, PL, ES, UK)	HCP Survey	Specialists with drug experience	340	246 (100.0)	Receipt, use, knowledge	Submission of FSR to EMA/PRAC as part of PSUR update	Changes to aRMM / Improve distribution of aRMM or re-distribute / FU Survey / awaiting further results or discussion

NOTE: Only references for studies with FSRs available in the EU PAS Register are provided. The remaining are kept on file as they were provided by MAHs or by EMA via freedom of information requests.

a-RMP Study Categories (GVP V[25]):
- Category 1: imposed as an obligation in accordance with REG Art 9(4)(cb) and Art 10a(1)(a) and with DIR Art 21a(b) and Art 22a(1)(a) (category 1 of studies in GVP Module V);
- Category 2: imposed as a specific obligation in the framework of a marketing authorisation granted under exceptional circumstances
- Category 3: required in the risk management plan (RMP) to investigate a safety concern or to evaluate the effectiveness of risk minimisation activities
- Other: conducted voluntarily by a marketing authorisation holder

b-the upper extreme of the interval was used to calculate the percentage
c-the lower extreme of the interval was used to calculate the percentage
d-Data extracted from Study Protocol
e-Given the variability of terms used across FSRs to name endpoints, the categories presented here relate to what is asked in the question and not the term used in the study documents. We have created 5 survey dimensions (receipt, use, reading, knowledge, behaviour) and assigned process indicators/questions to these.
*if these data were not available from FSRs or protocols, the product Summary of Products Characteristics and the EPAR were searched and used as additional sources of information.

Abbreviations: ADHD: attention deficit hyperactivity disorder; aRMM: additional risk minimisation measure; DHPC: dear healthcare professional communication; FSR: final study report; GP: general practitioner; HCP: healthcare professional; PASS: post-authorisation safety study; PSUR: Periodic safety update report; RMM: risk minimisation measure; RMP: risk management plan

Table S2. List of RMEv/products and studies included (Objective 3)

Product / RMEv	Type of aRMM evaluated					Safety Concerns targeted by aRMM	Study Ref.	Measures of effectiveness in RMEv		Study Design	Participating Countries [a]	Data Source	N. Included and Data Periods	Source
	HCP brochure, leaflet or guide	DHPC	HCP Checklist	Patient brochure, leaflet or guide	Patient card			Process Indicators	Outcomes					
Quetiapine (N05A H04)	Educational materials at new safety precaution in Jan-Nov 2012					Extrapyramidal symptoms Somnolence Weight gain Lipid changes Hyperglycaemia Metabolic risk factors, metabolic syndrome	[71]	Receipt, use (reading), self-reported behaviour	-	One-wave Survey Post-implementation	8 (AT, DE, HU, IT, ES, RO, UK, SE)	HCP Survey	800 GPs, specialists with and w/o drug experience	FSR
	x						[72]	-	Behavioural Outcomes (Frequency of monitoring metabolic parameters)	Retrospective Post-implementation	1 (UK)	EMS Disease Analyser	93 UK GP practices (887 patients) from 11 January to 31 July 2012	FSR
											1 (DE)	EMS Disease Analyser	42 Psychiatry and 145 Neurology practices (6153 patients) from 13 February to 31 August 2012	
Cyproterone acetate /ethinylestradiol (CPA/EE) containing products (G03)	DHCP in Jun-2013, educational material for HCPs, the Patient Information Card and Prescriber Checklist					Revised indication: For the treatment of acne only (alopecia dropped) CPA/EE should be used only after topical therapy or systemic antibiotic treatments have failed. CPA/EE should not be used in combination with other hormonal contraceptives New safety precautions; thromboembolic complications	[73]	Knowledge, self-reported behaviour	-	One-wave Survey Post-implementation	1 (DE)	HCP Survey	32 GPs	Summary FSR
							[74]	-	Behavioural Outcomes (Frequency of off label use)	Retrospective Pre- and post-implementation	1 (NL)	PHARMO	15252 New CPA/EE users in 2011 and 2012	Interim Report only
											1 (UK)	THIN	5683 New CPA/EE users in 2011 and 2012	
		x	x		x						1 (IT)	HSD	928 New CPA/EE users in 2011 and 2012	
							[75,76]	Knowledge, receipt	-	One-wave Survey Post-implementation	5 (AU, CZ, FR, NL, ES)	HCP Survey	759 GPs with drug experience	FSR, manuscript, poster
							[77]	-	Behavioural Outcomes (Frequency of off-label use)	One-wave Survey Post-implementation	5 (AU, CZ, FR, NL, ES)	Drug Utilisation Survey of HCPs and patients	1513 patients by 120 physicians from the specialties gynaecology and dermatology, as well as GPs	FSR
Ipilimumab (L01XC11)	Patient Information Brochure, Patient Alert Card, HCP Frequently Asked Questions Brochure at drug approval in Jul 2013					Gastrointestinal (GI) infusion-related adverse reactions (irARs) (e.g. diarrhoea, colitis, GI perforation) Hepatic irARs (e.g., hepatitis) Skin irARs (e.g., rash, pruritus) Neurologic irARs (e.g., neuropathy) Endocrine irARs (e.g., hypopituitarism, hypothyroidism, adrenal insufficiency) Other irARs (e.g., pneumonitis, nephritis, non-infective myocarditis, pancreatitis, uveitis)	[78]	Awareness, receipt, use (reading), knowledge, self-reported behaviour	- Health Outcomes (Rate of irAR for GI, hepatic, skin, neurological and endocrine risks) via spontaneous reporting.	One-wave Survey Post-implementation	10 (AU, BE, FR, DE, IE, IT, ES, SE, NL, UK)	HCP and Patient Surveys	88 Specialists, with drug experience,/ 27 patients/caregivers	FSR
	x			x	x					Retrospective Post-implementation		Company Global Drug Safety database	ipilimumab users	
Trimetazidine (C01EB15)	DHPC at suspension of ophthalmology and otolaryngology indications in Sep 2012					Use of trimetazidine restricted to an add-on therapy for patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line anti-anginal therapies. Ophthalmology and otolaryngology (ENT) indications suspension.	[79]	Receipt, knowledge, self-reported behaviour (Proportion of prescriptions)	-	One-wave Survey Post-implementation	12 (BG, CZ, EE, FR, HU, LV, LT, PL, PT, RO, SK, ES)	HCP Survey (+aggregated prescription data)	1123 GPs, specialists with and w/o drug experience	FSR
							[80]	-	Behavioural Outcomes (Proportion of prescriptions for each indication over time)	Retrospective Pre- and post-implementation Before the restriction of trimetazidine to cardiology: from July 2011 to June 2012 6 months after DHPC sending: from April 2013 to March 2014	1 (RO)	National Diagnostic Index	All prescriptions of trimetazidine made by GPs, ophthalmologists and ENT specialists in outpatient settings	Summary FSR
											1 (FR)	IMS Prescribing Insights		
											1 (GR)	IMS Prescribing Insights		
											1 (PL)	IMS Prescribing Insights		
		x									1 (ES)	IMS Prescribing Insights		
							[81]	-	Behavioural Outcomes (proportion of prescriptions of	Retrospective Pre- and post-implementation,	1 (HU)	National Prescription Audit	775,859 prescriptions the reference period and 849,855 in the assessment period, by ENT specialists, ophthalmologists, cardiologist and GPs/other,	Summary FSR

Product / RMEv	Type of aRMM evaluated					Safety Concerns targeted by aRMM	Study Ref.	Measures of effectiveness in RMEv		Study Design	Participating Countries [a]	Data Source	N. Included and Data Periods	Source
	HCP brochure, leaflet or guide	DHPC	HCP Checklist	Patient brochure, leaflet or guide	Patient card			Process Indicators	Outcomes					
									trimetazidine for ophthalmological or ENT diagnoses among the total prescriptions of trimetazidine after the restriction of its indications.	24-month reference period: July 2010 - June 2012 24-month assessment period: April 2013 - March 2015	1 (RO)	National Diagnostic Index	5,105,121 prescriptions in the reference period and 10,440,159 in the assessment period, by ENT specialists, ophthalmologists, cardiologist and GPs/other,	
											1 (FR)	IMS Prescribing Insights	1,936 (reference period) and 371 (assessment period) prescriptions were included in the study, by ENT specialists, ophthalmologists, cardiologist and GPs/other,	
											1 (ES)	IMS Prescribing Insights	713 (reference period) and 535 (assessment period) prescriptions, by ENT specialists, ophthalmologists, cardiologist and GPs/other,	
Domperidone-containing medicines (A03FA03)	DHPC after review of product information to strengthen cardiac adverse effects, Apr-Sep 2014					Cardiac risk - QT prolongation: restriction of the indication to nausea and vomiting; · recommended limitation of duration for usual use to 7 days; · reduction of the maximum daily dose to 10 mg TID for adults and adolescents; reduction of the maximum daily dose to 0.25 mg/kg TID for neonates, infants, children (less than 12 years of age), and adolescents weighing less than 35 kg; - measuring devices should be included with liquid formulations to allow accurate dosing by bodyweight; contraindication of the combination with other drugs that increase the cardiac risks by themselves or increase the plasma level of domperidone; and · contraindication in patients with moderate or severe hepatic impairment or certain cardiac conditions.	[82,154]	-	Behavioural Outcomes (Composite endpoint consisting of: Prescribing for on-label indication; o Duration of use ≤7 days; o Dose no higher than recommended; o No concomitant use of medications that prolong the QT-interval or are potent CYP3A4 inhibitors; and No prescribing to patients with contraindicated conditions, e.g., moderate or severe liver disease, underlying cardiac diseases.	Retrospective Pre- and post-implementation Background period: 1 January 2011 to 31 March 2013 1-year pre-implementation period: 1 April 2013 to 31 March 2014 6-month implementation period: 1 April 2014 to 30 September 2014 1-year post-implementation period: 1 October 2014 to 30 September 2015	1 (BE)	Quintiles IMS	53,575 adult prescriptions (37,098 pts) 9,949 paediatric prescriptions (7,704 pts) 66 for patients aged 12-14 years weighing less than 35 kg (54 pts)	FSR
											1 (FR)	Quintiles IMS	324,213 adult prescriptions (194,118 pts) 75,465 paediatric prescriptions (56,764 pts) 1,491 prescriptions for patients aged 12-14 years weighing less than 35 kg (1,160 pts)	
											1 (DE)	Quintiles IMS	27,173 adult prescriptions (9,192 patients) 6 paediatric prescriptions (6 patients) 1 prescription for patients aged 12-14 years weighing less than 35 kg (1 patient)	
		x									1 (ES)	Quintiles IMS	102,494 adult prescriptions (21,713 patients); 3,425 paediatric prescriptions (2,939 patients) 49 prescriptions for patients aged 12-14 years weighing less than 35 kg (34 patients)	
											1 (UK)	CPRD	532,884 adult prescriptions (109,767 patients); 17,382 paediatric prescriptions (3,038 patients) 141 prescriptions for patients aged 12-14 years weighing less than 35 kg (52 patients)	
							[83,154]	Receipt, knowledge		One-wave Survey Post-implementation	5 (FR, DE, UK, BE. ES)	HCP Survey	1805 GPs, specialists with drug experience	FSR
Abatacept (L04AA24)	Patient alert cards for each formulation at drug approval in May 2007					Infections with special reference to TB and patients with COPD Screening for tuberculosis prior to administration of abatacept Screening for viral hepatitis prior to administration of abatacept Infusion-related reactions (intravenous abatacept) Injection reactions (subcutaneous abatacept)	[84]	Awareness, receipt, use, reading, knowledge, self-reported behaviour	Health outcomes (Proportion of infections)	One-wave Survey Post-implementation	5 (FR, DE, ES, SE, UK)	HCP and patient Surveys	79 specialists, nurses with drug experience patients/carers, 190 patients	FSR
					x					Retrospective Post-implementation		Medical records data	181 patients receiving abatacept within 3 prior months	
Apixaban (B01AF02)	Prescriber Guide and Patient alert card in Sep 2012 at approval of new indication (atrial fibrillation) and later updated to include new indications. As of April 2015, a revised patient alert card was included inside the packaging					Bleeding Liver injury Severe renal or hepatic impairment	[85]	Receipt, use, reading, knowledge, self-reported behaviour	Health Outcomes (Proportion of preventable bleeding)	Retrospective post-implementation	10 (AU, BE, DK, FR, DE, IT, NO, ES, SE, UK)	Company Global Drug Safety database		FSR
	x				x					One-wave Survey post-implementation		HCP and patient Surveys	370 GPs, specialists, nurses, pharmacists, patients, carers / 125 patients	

Product / RMEv	Type of aRMM evaluated					Safety Concerns targeted by aRMM	Study Ref.	Measures of effectiveness in RMEv		Study Design	Participating Countries [a]	Data Source	N. Included and Data Periods	Source
	HCP brochure, leaflet or guide	DHPC	HCP Checklist	Patient brochure, leaflet or guide	Patient card			Process Indicators	Outcomes					
Florbetapir (V09AX05)	Reader training materials					PET reading errors	**Ongoing Study** [86]	Knowledge, self-reported behaviour	Behavioural Outcomes (Frequency of reading errors)	One-wave Survey post-implementation	3 (UK, ES, IT)	HCP Survey	Physicians: N not yet available	Not yet available
	x													
Agomelatine (N06AX22)	A physician guide was implemented at time of authorisation. Updated physicians' guides were distributed in Europe, and DHCP were sent in 2012 and 2013. In 2014 messages reinforced by redistribution of prescriber guide and implementation of patient booklet					Hepatotoxic reactions	[87]	Self-reported Behaviour, knowledge and receipt	Behavioural Outcomes (liver testing)	Retrospective pre/post Pre- and post-implementation The 'before-RMM' period January 2013 to November 2014 . The 'after-RMM' period: February–August 2015 to November 2016	4 (DK, FR, DE and ES)	Medical records data	54 sites (21 GPs and 33 specialists) recruited 437 patients in the before-RMM period and 404 patients in the after-RMM period (35 patients contributed data to both periods)	Manuscript
	x	x		x						One-wave Survey post-implementation		Patient Survey	237 patients	
Rituximab (L01XC02)	HCP education leaflet, patient alert cards and patient education leaflets in May 2009					Infections, especially Progressive Multifocal Leukoencephalopathy	[70,88]	Self-reported Behaviour, knowledge and receipt, use (reading)	Behavioural Outcomes (proportion of patients treated with MabThera off-label)	One-wave Survey Post-implementation	5 (FR, DE, IT, ES, UK)	Patient Survey	524 patients receiving MabThera for non-oncology indications at infusion centres	Summary Report, manuscript
	x			x	x					Retrospective Post-implementation		Medical records data	1012 patients receiving MabThera for non-oncology indications at infusion centres	
Valproate and related substances (N03AG01)	DHPC and educational materials for HCPs after review that let to strengthened warnings in Nov 2014					Use of valproate in female patients due to the risk of malformations and developmental problems in children exposed to the drug in utero	[89]	Receipt, knowledge, self-reported behaviour	-	One-wave Survey Post-implementation	5 (FR, DE, ES, SE, UK)	HCP survey	1153 physicians who prescribed valproate	FSR
	x	x					[90]	-	Behavioural Outcomes (Proportion of off-label use; Health outcomes (pregnancy cases)	Retrospective Pre- and post-implementation 36-month period before the implementation: Jan 2012 to Dec 2014 36-month period after the implementation, depending on date of distribution of DHPC and educational materials	1 (FR)	IMS Disease Analyser	21-month pre-implementation period: ranged from 1,683 patients with 14,403 valproate prescriptions in Spain to 14,287 patients with 184,606 valproate prescriptions in Sweden. Post-implementation period: 1,839 patients with 21,261 prescriptions in Spain to 14,444 patients with 257,573 prescriptions in Sweden.	Summary Report
											1 (DE)	IMS Disease Analyser		
											1 (SE)	National Health Registries		
											1 (ES)	IMS LPD		
											1 (UK)	CPRD		
							[91]	-	Behavioural Outcomes (prevalence of valproate prescribing over time, frequency of indications)	Retrospective Pre- and post-implementation, 6-month periods 01/01/2010-30/06/2015	1 (UK)	CPRD	Women aged 14-45 years receiving valproate	ISPE Abstract
Rivastigmine (N03AG01)	Patient reminder card, comprised of the Instructions for Use and the Medication Record Sheet at approval of new patch strength in Mar 2013					Multiple patch use which may result in overdose (medication error)	[92]	Use, helpfulness	Behavioural Outcomes (proportion of inappropriate use)	Prospective Post-implementation Prior to study data (i.e. years up to the enrolment visit) collected at baseline via medical chart abstraction	4 (DE, GR, PT, and UK)	Primary data collection	659	FSR
					x									
Vismodegib (L01XX43)	Pregnancy prevention program: DHPC, HCP reminder card, patient alert card, patient brochure, HCP brochure at conditional drug approval in Jul 2013					Teratogenicity – prevention of foetal exposure	[70]	Knowledge, self-reported behaviour, use	Health Outcomes (Proportion of pregnancy cases)	One-wave Survey Post-implementation	1 (UK)	HCP survey	31	Manuscript
	x	x		x	x					Retrospective Post-implementation, 30 January 2014 to 29 July 2014		Company Global Drug Safety database	1500 Erivedge treated patients	

Product / RMEv	Type of aRMM evaluated					Safety Concerns targeted by aRMM	Study Ref.	Measures of effectiveness in RMEv		Study Design	Participating Countries [a]	Data Source	N. Included and Data Periods	Source
	HCP brochure, leaflet or guide	DHPC	HCP Checklist	Patient brochure, leaflet or guide	Patient card			Process Indicators	Outcomes					
Trastuzumab emtansine - Kadcyla (L01XC14)	HCP booklet and HCP key points to remember leaflet. Specific UK measures: take-care poster, feedback questionnaire, company pre-paid envelopes at drug approval in Nov 2013					Medication errors from name confusion could lead to dosing errors and serious ADRs in patients.	[70]	Knowledge, helpfulness	Behavioural Outcomes (Proportion of medication error cases Health Outcomes (Number of spontaneously reported medication error)	One-wave Survey Post-implementation	1 (UK)	HCP feedback questionnaires	68	Manuscript
	x									Retrospective Post-implementation, 22 February 2014 to 21 August 2014		Company Global Drug Safety database	6519 Kadcyla treated patients	
Dabigatran etexilate (B01AE07)	Prescriber guide and a patient alert card at approval of new indication (atrial fibrillation) in Aug 2011 Safety Update in Nov 2011					Bleeding for new indication (Stroke Prevention in Atrial Fibrillation (SPAF) indication)	[93]	Awareness, receipt, use, reading, knowledge	-	One-wave Survey Post-implementation	8 (UK, DE, ES, FR, DK, BG, CZ, SK)	HCP and Patient Surveys	411 GPs, specialists with drug experience, patients / 802 pts	FSR
	x				x	Low doses should be prescribed to elderly patients. Importance of monitoring of renal function, in particular in patients over 75 years	[94]	-	Health Outcomes (Incidence of major bleeding) Behavioural Outcomes (proportion of inappropriate prescribing)	Retrospective Post-implementation, first prescription in the period 1 August 2011 to 30 June 2014	1 (DK)	National Health Registries	21221	Manuscript
Belatacept (L04AA28)	Patient alert card at drug approval in Jun 2011					Post-Transplant Lymphoproliferative Disease Serious infections Serious viral infection Serious herpes infections Serious citomegalovirus infections Serious polyoma infections CNS infections Serious fungal infections Tuberculosis Progressive Multifocal Leukoencephalopathy	**Ongoing Study** [95]	Awareness, receipt, use, reading, knowledge, self-reported behaviour	Health Outcomes (Proportion of serious infections)	One-wave Survey post-implementation	4 (AU, FR, DE, SE)	HCP and Patient Surveys	Not yet available	Not yet available
					x					Retrospective post-implementation		Medical records data	Not yet available	Not yet available
Methoxyflurane (N02BG09)	HCP administration guide and checklist, and in the patient alert card at drug approval in Oct 2015					Hepatotoxicity, nephrotoxicity	**Ongoing Study** [96]	-	Health Outcomes (Proportion of hepatotoxicity, nephrotoxicity) Behavioural Outcomes a (Proportion of off-label use / medication errors)	Prospective post-implementation	1 (UK)	Primary data collection	Not yet available	Not yet available
	x		x		x		**Ongoing Study** [97]	awareness, usage, readability, knowledge and understanding, self-reported behaviour	-	One-wave Survey post-implementation		HCP and Patient Surveys	Not yet available	Not yet available
Thiocolchicoside-containing products (M03BX05)	DHPC and educational materials for HCPs and patients after safety referral in Jan 2014					Teratogenicity, embryotoxicity, spontaneous abortion, impaired male fertility and cancer	[98]	knowledge, usage, receipt, self-reported behaviour	-	One-wave Survey Post-implementation	4 (FR, GR, IT, PT)	HCP Survey	651 GPs, rheumatologists, orthopaedists	FSR
	x	x		x			**Ongoing Study** [99]	-	Behavioural Outcomes	Retrospective Pre- and post-implementation			Not yet available	Not yet available

Product / RMEv	Type of aRMM evaluated					Safety Concerns targeted by aRMM	Study Ref.	Measures of effectiveness in RMEv		Study Design	Participating Countries [a]	Data Source	N. Included and Data Periods	Source
	HCP brochure, leaflet or guide	DHPC	HCP Checklist	Patient brochure, leaflet or guide	Patient card			Process Indicators	Outcomes					
									(Proportion of off-label use)					

[a] Countries participating in the study. Country acronyms: AU (Austria); BE (Belgium); BG (Bulgaria); CZ (Czech Republic); DE (Germany); DK (Denmark); EE (Estonia); ES (Spain); FR (France); GR (Greece); HU (Hungary); IE (Ireland); IT (Italy); LT (Lithuania); LV (Latvia); NL (Netherlands); PL (Poland); PT (Portugal); RO (Romania); SE (Sweden); SK (Slovakia); UK (United Kingdom)

Abbreviations: aRMM: additional risk minimisation measure; CPRD: Clinical Practice Research Datalink; CPA/EE: cyproterone acetate/ethinylestradiol; DHPC: dear healthcare professional communication; ENT: otolaryngologist; FSR: final study report; GI: gastrointestinal; GP: General Practitioner; HCP: healthcare professional; irARs: infusion-related adverse reactions; RMEv: risk minimisation evaluation; SPAF: Stroke Prevention in Atrial Fibrillation

Table S3. List of RMEv with results of process indicators (Objective 3)

Product / RMEv	Study Population	aRMM	% Receipt of the aRMM	% Reading the aRMM (among those who received)	% Use of the aRMM (among those who received)	% Correct Knowledge of Key Safety Risk	% Correct Self-reported Behaviour around Key Safety Information
Quetiapine (N05A H04)	HCPs	Educational material	37% [71]	91% [71]	-	-	~70% monitored patients [71]
CPA/EE containing products products (G03)	HCPs	DHPC	46% [75]	-	-	Increased risk of venous and/or arterial thrombotic events [73] 100% Symptoms of deep vein thrombosis, pulmonary embolism, and cerebrovascular accident; most important risk factors for thrombosis; instructions of use in smokers; and approved indication for moderate-severe acne [75] >80% Approved indication for hirsutism [75] 69% Prescribing CPA/EE for acne only after failure of topical therapy or systemic antibiotics [75] 48%	• None of the physicians indicated they used the product as sole hormonal contraceptive or combined it with other oral hormonal contraceptives [73] • 88% indicated they only used the product in women of reproductive age [73] • None said they used the product in women with alopecia [73] • 91% informed that they used the product in women with moderate to severe androgen sensitive acne, if local or systemic antibiotics had not worked [73] • 28% replied they did not use the product in women with hirsutism [73]
		Patient card	16% [75]				
		Prescriber Checklist	17% [75]				
Ipilimumab (L01XC11)	HCPs	HCP frequently asked questions brochure	47% [78]	78% [78]	97% [78]	Colitis [78] 96% Hepatitis [78] 85% Toxic necrosis[78] 71% Neuropathy [78] 67% Inflammation of the eye [78] 67%	Monitored irARs [78] 86% Appropriate actions should an irAR be identified [78] 86% Educate patients about the need to report symptoms [78] 88% Educate patients about symptoms of irARs [78] 62%
		Patient Brochure	96% [78]	-	96% [78]		
		Patient card	96% [78]	93% [78]	80% [78]		
	Patients	Patient brochure	67% [78]		83% [78]	Colitis [78] 41% Hepatitis [78] 44% Toxic necrosis [78] 44% Neuropathy [78] 22% Inflammation of the eye [78] 41% Endocrine [78] 37%	Immediate notification of potential irARs [78] 96% Appropriate actions should an irAR be identified [78] 86%
		Patient card	59% [78]		56% [78]		
Trimetazidine (C01EB15)	HCPs	DHPC	35% [79]	-	-	Angina pectoris: 74% (weighted) [79]	34% of all prescriptions were as an add-on therapy for patients with stable angina pectoris inadequately controlled by or intolerant to first-line anti-anginal therapies [79]
Domperidone (A03FA03)	HCPs	DHPC	47% [83]	-	-	Nausea and vomiting [83] 80% Restriction of indication to minimise cardiac risk: Recommended limitation of duration for usual use to 7 days [83] 70% Restriction of indication to minimise cardiac risk: Maximum Daily Dose for Adults and Adolescents (12 years of age and older and weighing 35 kg or more) [83] 84% Restriction of indication to minimise cardiac risk: Maximum Daily Dose for Neonates, Infants, Children (less than 12 years of age) and Adolescents weighing less than 35 kg [83] 37% Restriction of indication to minimise cardiac risk: concomitant use of drugs that prolong the QT interval and drugs that are potent CYP3A4 inhibitors [83] 26% Restriction of indication to minimise cardiac risk: Prolongation of cardiac conduction intervals, particularly QTc [83] 87% Restriction of indication to minimise cardiac risk: Moderate to severe hepatic impairment [83] 48%	-
Abatacept (L04AA24)	HCPs	Patient card	68% [84]	72% [84]	72% [84]	Infections [84] 85% Pre-screening for tuberculosis [84] 85% Pre-screening for hepatitis [84] 73%	Informed them about side effects [84] 96% Writes down the date of treatment in the patient card [84] 54% Overall behaviour [84] 74%
	Patients	Patient card	57% [84]	84% [84]	65% [84]	Infections [84] 56% Pre-screening for TB [84] 78% Pre-screening for hepatitis [84] 47%	Informed them about side effects [84] 66% Seek for immediate medical attention when fever [84] 69% Seek for immediate medical attention when chest tightness [84] 81% Seek for immediate medical attention when wheezing [84] 66% Seek for immediate medical attention when severe dizziness or feeling light-headed [84] 64% Overall behaviour [84] 68%

Table S3. List of RMEv with results of process indicators (Objective 3)

Product / RMEv	Study Population	aRMM	% Receipt of the aRMM	% Reading the aRMM (among those who received)	% Use of the aRMM (among those who received)	% Correct Knowledge of Key Safety Risk		% Correct Self-reported Behaviour around Key Safety Information	
Apixaban (B01AF02)	HCPs	Patient card	55% [85]	-	88% patients has been provided with or given access to patient card [85]	Patients with severe renal impairment (CrCl 15-29 mL/min) at increased risk of bleeding complications [85]	82%	Discuss the need to seek immediate medical attention for a bleeding event with patients [85]	80%
						Patients taking strong inhibitors of both CYP3A4 and P-gp at increased risk of bleeding complications [85]	64%	Displayed behaviour that was considered 'ideal' in response to the hypothetical case study scenarios [85]	62%
						Patients taking oral contraception at increased risk of bleeding complications when treated with drug [85]	66%		
		Prescriber Guide	59% [85]	98% [85]	75% [85]	Patients who have recently undergone brain, ophthalmic or spinal surgery at increased risk of bleeding complications [85]	72%		
						Patients taking NSAIDs including acetylsalicylic acid at increased risk of bleeding complications [85]	86%		
						Patients with recent gastrointestinal ulceration at increased risk of bleeding complications [85]	89%		
	Patients	Patient card	53% [85]	91% [85]	94% [85]	Bleeding: 71% [85]		Seek immediate medical attention for a bleeding event [85]	86%
								Showed the PAC to every doctor or dentist before any treatment [85]	42%
Agomelatine (N06AX22)	Patients	Patient Booklet	Assessed but not available	-	-	Hepatotoxicity: 73% [87]		77% had a blood test ordered brefore treatment; 63% identified that the test was to check liver function. 82% had a blood test during treatment; 78% identified that the test was to check liver function [87]	
Rituximab (L01XC02)	Patients	Patient card	33% [88]	80% [88]	-	PML: 72% [88]		70% of patients answered 'when I noticed symptoms, I talked to my doctor" [88]	
Valproate and related substances (N03AG01)	HCPs	DHPC	60% [89]	-	-	Informed about the risk of taking drug during pregnancy: 92% [89]		-	
	HCPs	Educational Material	30% [89]	-	-				
Rivastigmine (N03AG01)	Patient Assistants	Patient Reminder Card Medication Record Sheet	Assessed but not available	-	38%	-		-	
Vismodegib (L01XX43)	HCPs	PPP (DHPC, HCP reminder card, PAC, Patient brochure, HCP brochure)	-	-	68% (provide materials to patients) 74% (patients to complete verification of counselling form) [70]	Teratogenicity: 90% [70]		Pregnancy testing in women of childbearing potential [70]	84%
								Compliance with contraception in women of childbearing potential [70]	84%
								Contraceptive counselling [70]	79%
								Educate male patients on the use of condoms [70]	79%
								Report pregnancies to the Company [70]	74%
								Refer patient to a specialist obstetrician in the event of pregnancy [70]	74%
								Limit prescriptions to 28 days of treatment. Continuation of treatment should require a new prescription [70]	58%
Trastuzumab emtansine (L01XC14)	HCPs	HCP booklet/ Healthcare professional key points to remember leaflet / Take-care poster Feedback questionnaire Company pre-paid envelopes	-	-	-	Medication errors: 93% [70]		-	
Dabigatran etexilate (B01AE07)	HCPs	Patient card	65% [93]	-	89% [93]			-	
		Prescriber Guide	71% [93]	97% [93]	-			-	
	Patients	Patient card	56% [93]	90% [93]	-	Bleeding: 53% [93]		-	

Abbreviations: aRMM: additional risk minimisation measure; CPRD: Clinical Practice Research Datalink; CPA/EE: cyproterone acetate/ethinylestradiol; DHPC: dear healthcare professional communication; ENT: otolaryngologist; FSR: final study report; GI: gastrointestinal; GP: General Practitioner; HCP: healthcare professional; irARs: infusion-related adverse reactions; RMEv: risk minimisation evaluation; SPAF: Stroke Prevention in Atrial Fibrillation

Table S4. Summary of results of behavioural outcomes

Product / RMEv	Study Ref	Outcomes / Results		Overall	UK	Germany	Romania	France	Greece	Poland	Spain	Hungary	Italy	Sweden	Portugal
Quetiapine	[72]	Proportion of patients monitored of weight at least once			38.7%	0.4%									
		Proportion of patients monitored of cholesterol at least once			27.7%	1%									
		Proportion of patients monitored of hyperlipidaemia at least once			31.9%	0.7%									
		Proportion of patients with diabetes monitored of signs and symptoms of hyperglycaemia at least once			50.6%	0%									
		Proportion of patients at risk of diabetes monitored of cholesterol at least once			34.4%	6.9%									
		Proportion of patients with lifestyle counselling at least once			30.8%	0%									
		Proportion of practices monitored ≥50% of their relevant patients			16 to 67%	< 2%									
Trimetazidine	[80]	Proportion of prescriptions of trimetazidine for ophthalmological or otolaryngological diagnoses among the total prescriptions of trimetazidine after the restriction of its indications (assessment - reference period)	Reference Period				0.07% to 0.06%	Not reported	Not reported	1.6 to 2.2%	Not reported				
			Assessment Period												
		Change in absolute number of prescriptions issued (assessment - reference period)	Reference Period				Not reported	- 61% in otolaryngologist to -76% in GPs	-67% in GPs	Not reported	-26% in GP -57% in otolaryngologist				
			Assessment Period												
	[81]	Proportion of prescriptions of trimetazidine for ophthalmological or otolaryngological diagnoses among the total prescriptions of trimetazidine after the restriction of its indications (assessment - reference period)	Reference Period				0.1%	49.1%			78.1%	0.9%			
			Assessment Period				0.1%	52.8%			66.4%	0.6%			
		Change in absolute number of prescriptions issued (assessment - reference period)	Reference Period				absolute diff.: -0.0% relative diff.: -20.1%	abs. diff.: +3.7%.			absolute diff.: -11.8%	absolute diff.: -0.4% / relative diff.: -38.4%			
			Assessment Period												

Product / RMEv	Study Ref	Outcomes / Results		Overall	UK	Germany	Romania	France	Greece	Poland	Spain	Hungary	Italy	Sweden	Portugal
Domperidone	[82]	Proportion of domperidone prescriptions before and after implementation of the risk minimisation measures regarding the composite endpoint, which consisted of the following components (label requirements): prescribing for on-label indication, duration of use ≤7 days, dose no higher than recommended, no concomitant use of medications that prolong the QT-interval or are potent CYP3A4 inhibitors, and no prescribing to patients with selected contraindicated conditions.		**Optimistic Scenario**: moderate improvement in compliance with all label requirements was observed for most countries, with the exception of France, which demonstrated a large improvement.											
				Intermediate scenario A Inconclusive: Risk ratios ranged from a small improvement in compliance (Belgium) to a large improvement in compliance (France), however, no conclusions could be drawn for Germany, Spain, or the UK due to the small proportions of prescriptions meeting all label requirements.										
				Intermediate scenario B The findings for intermediate scenario-B were mostly positive and ranged from a modest improvement in compliance (UK) to a large improvement in compliance (France, Germany), however, no conclusions could be drawn for Belgium or Spain due to the small proportions of prescriptions meeting all label requirements.										
				Pessimistic scenario: Inconclusive.										
Agomelatine	[87]	Proportion of patients with at least one liver test performed between 4 weeks before and 3 days after the initiation of agomelatine treatment	Before aRMM	24.1%										
			After aRMM	25.2%										
		Proportion of patients with at least one liver test performed between 2 and 28 weeks after treatment initiation and while on treatment	Before aRMM	56.3%										
			After aRMM	61.5%										
		Composite of the above	Before aRMM	15.1%										
			After aRMM	16.3%										
		Proportion of patients with At least one liver test before or at dose escalation, defined as within 1 week before or 1 week after dose escalation	Before aRMM	31.0%										
			After aRMM	44.8%										

Product / RMEv	Study Ref	Outcomes / Results		Overall	UK	Germany	Romania	France	Greece	Poland	Spain	Hungary	Italy	Sweden	Portugal
		Proportion of patients with At least one liver test after dose escalation, defined as 2–28 weeks after dose escalation and during treatment	Before aRMM	50.0%											
			After aRMM	67.2%											
		Composite of the above	Before aRMM	20.7%											
			After aRMM	39.7%											
Rituximab	[70,88]	Proportion of patients prescribed Mabthera for off-label non-oncology indications			16.50%	25.00%		29.90%			34.80%		43.40%		
Valproate and related substances	[90]	Proportion of valproate prescriptions with at least one medication used prior the valproate initiation and related to the valproate indication (epilepsy, bipolar disorder, migraine headaches) within 12 months before the valproate initiation date.	Pre-implementation		66.4%	47.9% in GPs; 49.4% in specialists		8.7%			78.0% in GPs; 87.4% in specialists			81.1%	
			Post-implementation		72.4%	47.0% in GPs; 49.1% in specialists		40.6%			78.2% in GPs, 85.6% in specialists			84.5%	
	[91]	Proportion of valproate prescribing in women aged 14-45 years over 6-month periods 01/01/2010-30/06/2015		17% decrease in valproate prevalence in the first half of 2015 compared to the first half of 2010 (0.28 vs. 0.23%)											
		Proportion of prescribing for epilepsy indication		-22%											
		Proportion of prescribing for bipolar disorder indication		-20%											
		Proportion of prescribing for migraine indication		-14%											
Rivastigmine	[92]	Proportion of inappropriate use of all doses as recorded by patients and/or their assistants	Prior to study	28%	61%	15%			41%						7%
			During study	18%	27%	16%			22%						6%
Dabigatran	[94]	Proportion of prescriptions to patients >75 years of high daily dose (150 mg bid) in relation to total number of prescriptions (110 and 150 mg bid) in this age group (incident users).		30% but then rapidly declined and later stabilised around 15% a year after the safety update											
Cyproterone acetate /ethinylestradiol (CPA/EE)	[77]	Proportion of patients with prescription indications for CPA/EE		The most frequent indication was acne with 66% of the prescriptions. The main reasons for prescription of CPA/EE were contraception (67%) and acne (66%).											
		Proportion of use of CPA/EE in accordance with the updated label		Prescriptions in 35% of patients reflect an approximation to accordance with the updated label of CPA/EE: 20% patients with a diagnosis of moderate to											

Product / RMEv	Study Ref	Outcomes / Results	Overall	UK	Germany	Romania	France	Greece	Poland	Spain	Hungary	Italy	Sweden	Portugal
			severe acne who had "previous topical and/or systemic antibiotic treatment" and those with hirsutism (15%).											
		Proportion of concomitant use of CPA/EE and other combined hormonal contraceptives,	The prescription of CPA/EE together with another hormonal contraceptive was 3%											
	[74]	Interim data available only												

Abbreviations: aRMM: additional risk minimisation measure; CPA/EE: cyproterone acetate/ethinylestradiol;

Table S5. List of EU RM Studies (Objectives 1, 2 and 3)

Fuente	Ref	Title / link	Drug name	Brand	Study Status	Process indicators	Behavioural or Health/Safety Outcomes	Thesis Objective
EU PAS	[155]	Evaluation of the effectiveness of risk minimisation measures: a survey among health care professionals and patient/caregivers to assess their knowledge and attitudes on prescribing and home administration conditions of velaglucerase alpha (vpriv®) in 6 European countries	velaglucerase alpha	Vpriv	ongoing	1		
EU PAS	[156]	Post Authorization Safety Study: Knowledge about safety precautions among physicians in Denmark prescribing CPA/EE products	CPA/EE		**Study 4**	1	1	Obj 1, Obj 2
EU PAS	[157]	Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study	CPA/EE	Diane-35	**Study 15**	1		Obj 1, Obj 2
ISPE Abstract	[158]	529. Evaluation of Risk Minimisation Activities for Cyproterone Acetate 2 mg/Ethinylestradiol 35 mg	CPA/EE	Diane-35	Du_Study 15	1		
Google		https://ichgcp.net/es/clinical-trials-registry/NCT02410031	CPA/EE	Diane-35	Du_Study 15	1		
EU PAS	[74]	Drug Utilization Study on Diane®-35 (and generics) in European healthcare databases	CPA/EE	Diane-35	**Study 75**		1	Obj 3
Google	[159]	https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.4319	CPA/EE	Diane-35	Du_Study 75			
ISPE Abstract	[160]	1095 | Reduction in use of Cyproterone/ Ethinylestradiol (Diane35 and generics) after risk minimisation measures in the Netherlands, UK and Italy	CPA/EE	Diane-35	Du_Study 75		1	
EU PAS	[77]	Drug Utilization Study on the Prescribing Indications for CPA/EE in 5 European Countries	CPA/EE	Diane-35	**Study 86**		1	Obj 3
EU PAS	[84]	Evaluation of the effectiveness of the abatacept (ORENCIA®) intravenous and subcutaneous formulation Patient Alert Cards in patients with rheumatoid arthritis in a sample of European Economic Area countries	abatacept	Orencia	**Study 22**	1	1	Obj 1, Obj 2, Obj 3
ISPE Abstract	[160]	1138 | Health care professional survey to assess the effectiveness of abatacept (Orencia®) patient alert cards in rheumatoid arthritis patients	abatacept	Orencia	Du_Study 22	1		
ISPE Abstract	[160]	440 | A novel approach to correlate soft and hard outcomes: Effectiveness of abatacept (Orencia®) patient alert cards in rheumatoid arthritis patients	abatacept	Orencia	Du_Study 22	1	1	
EU PAS	[161]	Evaluation of Physician and Patient Knowledge of Safety and Safe Use Information for Aflibercept in Europe: An Observational Post Authorisation Study	aflibercept	Eylea	**Study 25**	1		Obj 2
EU PAS	[162]	Evaluation of Physician Knowledge of Safety and Safe Use Information for Aflibercept Administered by Intravitreal Injection in Europe: A Follow-up Physician Survey	aflibercept	Eylea	ongoing	1		
EU PAS	[163]	Fabrazyme (agalsidase beta) home infusion educational materials effectiveness evaluation: a survey for healthcare providers and patients	agalsidase alfa	Fabrazyme	ongoing	1		
EU PAS	[164]	Agomelatine Drug Utilisation Study in Selected European Countries: A Multinational, Observational Study to Assess Effectiveness of Risk-Minimisation Measures	agomelatine	Valdoxan	**Study 37**	1	1	Obj 2, Obj 3
Pubmed	[87]	Agomelatine Drug Utilisation Study in Selected European Countries: A Multinational, Observational Study to Assess Effectiveness of Risk-Minimisation Measures	agomelatine	Valdoxan	Du_Study 37	1	1	
ISPE Abstract	[160]	500 | Agomelatine post authorization safety studies program: Comprehensive results	agomelatine	Valdoxan	Du_Study 37	1	1	
EU PAS	[165]	Myozyme (alglucosidase alfa) Safety Information Packet effectiveness evaluation: a health care professional survey	alglucosidase alfa	Myozyme	**Study 31**	1		Obj 2
ISPE Abstract	[160]	1132 | Pre/post effectiveness evaluation of the myozyme (alglucosidase alfa) safety information packet	alglucosidase alfa	Myozyme	Du_Study 31	1		
EU PAS	[166]	A drug utilization study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low LDL-C levels	alirocumab	Praluent	ongoing		1	
ISPE Abstract	[167]	806. Assessment of the Effect of Minimization Measures of the Risk of Stroke with Antipsychotic Use in Elderly Persons: A Nested Case-Control Study	antipsychotic		Study 79		1	
EU PAS	[85]	"Evaluation of the effectiveness of Eliquis® (apixaban) risk minimization tools in European	apixaban	Eliquis	**Study 23**	1	1	Obj 1, Obj 2, Obj 3
EU PAS	[148]	ABILIFY for the Adolescent Bipolar I Mania Indication of Tool Effectiveness Evaluation Strategy	aripiprazole	Abilify	**Study 14**	1		Obj, 1, Obj 2

Fuente	Ref	Title / link	Drug name	Brand	Study Status	Process indicators	Behavioural or Health/Safety Outcomes	Thesis Objective
Pubmed	[168]	Effectiveness Evaluation of Additional Risk Minimization Measures for Adolescent Use of Aripiprazole in the European Union: Results from a Post-Authorization Safety Study.	aripiprazole	Abilify	Du_Study 14	1		
EU PAS	[169]	Survey to evaluate the effectiveness of risk minimization measures for Atezolizumab use in the European Union	atezolizumab	Tecentriq	ongoing	1		
EU PAS	[142]	Physician Survey to Assess Effectiveness of Strattera Risk Minimisation Activities in Prescribers Treating Adult Patients with ADHD	atomoxetina	Strattera	**Study 7**	1		Obj 1, Obj 2
EU PAS	[143]	Physician Survey to Re-assess Effectiveness of Strattera Risk Minimisation Activities	atomoxetina	Strattera	**Study 8**	1		Obj 1, Obj 2
EU PAS	[170]	Quantitative Testing of Healthcare Provider Knowledge about YESCARTA® (axicabtagene ciloleucel) Risk Minimisation Measures	axicabtagene ciloleucel	Yescarta	ongoing	1		
EU PAS	[171]	Rheumatologist Survey to Assess the Effectiveness of the Risk Minimisation Measures (RMM) for Olumiant® (baricitinib) a JAK1/2 inhibitor	baricitinib	Olumiant	ongoing	1		
EU PAS	[95]	Evaluation of the effectiveness of the belatacept (Nulojix®) Patient Alert Card in patients following renal transplantation in European Economic Area countries.	belatacept	Nulojix	**ongoing**	1	1	Obj 3
EU PAS	[172]	A Cross-sectional Survey of Patients and Caregivers (20150228)	blinatumomab	Blincyto	**Study 89**	1		Obj 2
EU PAS	[173]	Survey of Physicians, Pharmacists, and Nurses Involved in the Prescribing, Preparation and Administration of Blincyto in Europe to Evaluate the Effectiveness of Additional Risk Minimization Measures (20150163)	blinatumomab	Blincyto	**Study 90**	1		Obj 2
Google	[174]	Evaluation of Risk Minimisation Measures for Blood Components – Based on Reporting Rates of Transfusion-Transmitted Reactions (1997–2013)	blood components		Study 82		1	
EU PAS	[175]	An international, observational retrospective data collection study assessing efficacy of applied risk minimisation measures in burn patients treated with NexoBrid	bromelains	NexoBrid	Study 45		1	
EU PAS	[176]	Healthcare Professional and Patient Surveys to Evaluate the Effectiveness of the Risk Minimisation Educational Materials for Certolizumab Pegol (CZP; CIMZIA®)	certolizumab	Cimzia	**Study 88**	1		Obj 2
EU PAS	[177]	Cilostazol Drug Utilisation Study	cilostazol	Ekistol	Study 46		1	
ISPE Abstract	[167]	712. Impact of Risk Minimization Measures on the Use of Cilostazol in Europe	cilostazol	Ekistol	Du_ Study 46		1	
Google	[178]	Impact of risk minimisation measures on citalopram use in two European countries	citalopram		Study 74		1	
Publication [107]	[179]	Prescription behavior for gastroprotective drugs in new users as a result of communications regarding clopidogrel–proton pump inhibitor interaction.	clopidogrel		Study 83		1	
EU PAS	[180]	A Prospective, Observational Drug Utilization Study of Cobicistat in Adults with HIV-1 Infection	cobicistat	Tybost	cancelled		1	
EU PAS	[181]	Drug utilisation study of risk minimisation measures for codeine using IMS electronic health records in Germany and France	codeine		ongoing		1	
EU PAS	[182]	A Cross-sectional Study to Evaluate the Effectiveness of the Colobreathe Risk Minimisation Educational Programme Among Healthcare Professionals and Patients	colistimethate Sodium	colobreathe	ongoing	1		
ISPE Abstract	[160]	956 | Assessment of colobreathe risk minimisation measures in the European Union: a cross-sectional study	colistimethate Sodium	colobreathe	ongoing	1		
EU PAS	[183]	Effectiveness of Xiapex® educational material for healthcare professionals in the treatment of Dupuytren's contracture - a non-interventional post-authorization safety study	collagenase	Xiapex	ongoing	1		
EU PAS	[184]	Effectiveness of Xiapex® educational material for healthcare professionals in the treatment of Peyronie's disease - a non-interventional post-authorization safety study	collagenase	Xiapex	ongoing	1		
EU PAS	[185]	Study of regulatory communication and risk awareness following the Article 31 referral of Combined Hormonal Contraceptives in relation to thromboembolism	contraceptives		Study 47		1	
EU PAS	[186]	Study of utilisation of combined hormonal contraceptives in Europe	contraceptives		ongoing		1	
EU PAS	[149]	A cross-sectional study to evaluate the effectiveness of XALKORI Patient Information Brochure among non-small cell lung cancer (NSCLC) patients receiving XALKORI treatment in Europe	crizotinib	Xalkori	**Study 16**	1		Obj 1, Obj 2
EU PAS	[150]	A cross-sectional study to evaluate the effectiveness of XALKORI Therapeutic Management Guide among physician prescribing XALKORI in Europe	crizotinib	Xalkori	**Study 17**	1		Obj 1, Obj 2

Fuente	Ref	Title / link	Drug name	Brand	Study Status	Process indicators	Behavioural or Health/Safety Outcomes	Thesis Objective
EU PAS	[93]	Post-authorisation study to evaluate the effectiveness of the risk minimisation activities in the treatment of SPAF	dabigatran	Pradaxa	**Study 3**	1		Obj 1, Obj 2, Obj 3
Pubmed	[94]	Evaluating the effectiveness of risk minimisation measures: the application of a conceptual framework to Danish real-world dabigatran data.	dabigatran	Pradaxa	**Study 48**		1	Obj 3
ISPE Abstract		523. A Framework for the Evaluation of the Effectiveness of Risk Minimisation Measures Applied to Retrospective Danish Real-World Dabigatran Etexilate Data	dabigatran	Pradaxa	Du_Study 48		1	
Google	[94]	d	dabigatran	Pradaxa	Du_Study 48		1	
EU PAS	[187]	RRA-19284 Survey of the Effectiveness of the DARZALEX® Educational Materials Regarding the Minimization of Risk of Interference for Blood Typing with Daratumumab	daratumumab	Darzalex	ongoing	1		
ISPE Abstract	[158]	981 | A survey among health care professionals to assess their knowledge and understanding on Darzalex® (daratumumab) educational materials regarding the risk of interference for blood typing in 12 European countries	daratumumab	Darzalex	Ongoing, only preliminary results available	1		
EU PAS	[145]	Survey of Oncology Practitioners Prescribing XGEVA® in Europe to Evaluate Their Knowledge of XGEVA® Summary of Product Characteristics Pertaining to Osteonecrosis of the Jaw (20110102)	denosumab	Xgeva	**Study 10**	1		Obj 1, Obj 2
EU PAS	[188]	Injectors' Survey to Assess Effectiveness of BELKYRA Risk Minimisation Activities	deoxycholic acid /dexamethasone	Belkyra	ongoing	1		
ISPE Abstract	[167]	800. Evaluation of Effectiveness of Risk Minimisation Measures Applied to the Use of Desmopressin by Elderly Patients in Denmark	desmopressin		Study 78		1	
EU PAS	[189]	Evaluation of the Physician Education Component of the Ozurdex Risk Management Plan	dexamethasone	Ozurdex	**Study 39**	1		Obj 2
EU PAS	[190]	A Multicentre, Non-interventional, Prospective, Observational Drug Utilisation Study of Ayendi Nasal Spray Prescribed as Treatment in Emergency Departments in the United Kingdom (UK)	diamorphine	Ayendi	Study 49		1	
EU PAS	[191]	Impact of EU label changes for systemic diclofenac products: post-referral prescribing trends	diclofenac		Study 50		1	
ISPE Abstract	[160]	954 | Are the risk minimization measures for diclofenac effective? A pre/post comparison based on German claims data	diclofenac		Du_Study 50		1	
ISPE Abstract	[160]	1098 | Impact of European label changes for systematic diclofenac products: Post-referral prescribing trends for initiation of systemic diclofenac products and time series regression	diclofenac		Du_Study 50		1	
EU PAS	[82]	A Drug Utilisation Study of Domperidone in Europe Using Databases	domperidone		**Study 51**		1	Obj 3
EU PAS	[83]	A Post-Authorisation Safety Study (PASS) to Assess the Effectiveness of the Risk Minimisation Measures of Domperidone – Physician Survey	domperidone		**Study 19**	1		Obj 1, Obj 2, Obj 3
ISPE Abstract	[158]	525. Assessment of Effectiveness of Dronedarone Risk Minimization Measures Through a Drug Utilization Study in Two European Countries	dronedarone	Multaq	Study 77		1	
EU PAS	[192]	Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study	edoxaban	Lixiana	Study 52		1	
EU PAS	[193]	An Observational Drug Utilization Study of Stribild® in Adults with HIV-1 Infection (GS-EU-236-0141)	elvitegravir/Cobicistat/Emtricitabine/Tenofovir	Stribild	Study 53		1	
EU PAS	[194]	Hemlibra Survey to Prescribers and Patients/Carers to Evaluate Awareness, Knowledge and Compliance to Additional Risk Minimization Measures	emicizumab	Hemlibra	ongoing	1		
EU PAS	[195]	GS EU 276 4027: A Cross Sectional Post Authorization Safety Study to Assess Healthcare Provider's Level of Awareness of Risk Minimisation Materials for Truvada® for Pre Exposure Prophylaxis in the European Union	emtricitabine tenofovir disoproxil	Truvada	**Study 35**	1		Obj 2
EU PAS	[196]	Survey on the knowledge and use of the Jext prescriber's checklist among physicians – a post-authorisation safety study	epinephrine	Jext	ongoing	1		
EU PAS	[197]	Assessment of Health Care Professionals' Knowledge and Behaviour Regarding Prescribing Conditions of Cholib® (fenofibrate and simvastatin fixed combination): A European PASS conducted in Austria, Portugal, Slovenia, Croatia, Greece and Bulgaria	fenofibrate / simvastatina	Cholib	ongoing	1		

Fuente	Ref	Title / link	Drug name	Brand	Study Status	Process indicators	Behavioural or Health/Safety Outcomes	Thesis Objective
EU PAS	[147]	Evaluation of the Effectiveness of Risk Minimisation Measures: A Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Instanyl® in France and the Netherlands	fentanil	instanyl	**Study 12**	1		Obj 1, Obj 2
ISPE Abstract	[167]	711. Evaluation of the Effectiveness of Risk Minimisation Measures: A Survey Among Health Care Professionals to Assess Their Knowledge and Attitudes on Prescribing Conditions of Instanyl® in France and the Netherlands	fentanil	instanyl	Du_Study 12	1		
EU PAS	[198]	A prospective observational study to assess effectiveness of the training and risk minimisation measures recommended for the usage of the diagnostic agent NeuraCeqTM in the post-authorisation clinical situation: A post-authorisation safety study (PASS)	florbetaben	NeuraCeq	ongoing		1	
EU PAS	[86]	Evaluation of Effectiveness of Amyvid Reader Training (I6E-AV-AVBE)	florbetapir	Amyvid	**ongoing**	1	1	Obj 3
EU PAS	[199]	Drug utilisation study (DUS) on flupirtine-containing medicinal products	flupirtine		Study 85		1	
EU PAS	[199]	Drug utilisation study (DUS) on flupirtine-containing medicinal products	flupirtine		Du_Study 85		1	
EU PAS	[200]	Drug utilisation study (DUS) on flupirtine-containing products Retrospective drug utilisation study using patient-level databases to characterise prescribing practices of flupirtine-containing drugs during routine clinical use and assess the main reasons for prescription by representative groups of prescribers	flupirtine		Study 91		1	
EU PAS	[201]	Post-Authorisation Safety Study (PASS) for Flupirtine – Effect of Risk Minimisation Measures in Germany	flupirtine		Study 92		1	
EU PAS	[202]	Post-Authorisation Safety Study (PASS) on Flupirtine-containing Medicinal Products - A retrospective, multicentre, non-interventional study to evaluate the effectiveness of the risk minimisation activities for flupirtine-containing medicinal products	flupirtine		Study 84		1	
EU PAS	[203]	Retrospective Chart Review to Evaluate the Effectiveness of the Risk Minimization Measures for the Use of Flupirtine 100 mg Immediate-Release Capsules in daily Practice	flupirtine		Study 54		1	
EU PAS	[204]	A Post-Authorisation Safety Study to Evaluate the Effectiveness of VIZAMYL™ Reader Training in Europe	flutemetamol	Vizamyl	ongoing		1	
EU PAS	[205]	WEUSKOP5233: Arixtra Physician Adherence to the Prescribing Information in isolated superficial vein thrombosis (SVT) Patients	fondaparinux	Arixtra	ongoing		1	
EU PAS	[206]	Effectiveness of the Additional Risk Minimization Measures in Conveying Safety Information to HCPs Dispensing, Administering or Prescribing Fosphenytoin	forphenytoin		ongoing	1		
EU PAS	[207]	Drug Utilization Study on the Risk Minimisation Tools for Sialanar	glycopyrronium bromide	Sialanar	ongoing		1	
Pubmed	[208]	Effectiveness of the golimumab educational program in ensuring healthcare professionals' awareness of risks described in the European risk management plan.	golimumab	Simponi	**Study 40**	1		Obj 2
Google	[208]	https://journals.sagepub.com/doi/full/10.1177/2042098619847420	golimumab	Simponi	Du_Study 40	1		
ISPE Abstract	[158]	528. Evaluation of Physician Awareness of Risks Described in the SIMPONI (Golimumab, GLM) EU-RMP Educational Program	golimumab	Simponi	Du_Study 40	1		
EU PAS	[209]	Impact of EU label changes for hydroxyzine products: post-referral prescribing trends	hydroxyzine		ongoing		1	
EU PAS	[210]	GS-EU-313-4226 A Cross-Sectional Post-Authorization Safety Study to Assess Healthcare Provider Awareness of Risks Associated with Zydelig® in the European Union	idelalisib	Zydelig	**Study 33**	1		Obj 2
EU PAS	[151]	Healthcare Professional and Patient Surveys to Assess the Effectiveness of Risk Minimisation Measures for Concentrated Insulin Lispro (Humalog 200 units/ml KwikPen; Liprolog 200 units/ml KwikPen)	Insulin Lispro		**Study 20**	1		Obj 1, Obj 2
Google	[211]	https://diabetes.diabetesjournals.org/content/68/Supplement_1/2324-PUB	Insulin Lispro		Du_Study 20	1		
EU PAS	[212]	Survey to evaluate the knowledge and understanding of the key safety messages in the healthcare professional guide and the patient guide for suliqua	Insulina glargina/lixisenatida	Suliqua	ongoing	1		
EU PAS	[78]	YERVOY Risk Minimisation Tool Evaluation Survey	ipilimumab	Yervoy	**Study 13**	1	1	Obj 1, Obj 2
Google		https://ichgcp.net/es/clinical-trials-registry/NCT02224768	ipilimumab	Yervoy	Du_Study 13	1		

Fuente	Ref	Title / link	Drug name	Brand	Study Status	Process indicators	Behavioural or Health/Safety Outcomes	Thesis Objective
Pubmed	[213]	Evaluation of compliance with isotretinoin PPP recommendations and exploration of reasons for non-compliance: Survey among French-speaking health care professionals and patients in Belgium.	isotretinoin		Study 55		1	
EU PAS	[214]	Isotretinoin and the effectiveness of the pregnancy prevention programmes in Europe	isotretinoin		Study 56		1	
EU PAS	[215]	Severe hypersensitivity reactions associated with iv iron containing medicinal products in countries of the European Economic Area – before and after implementation of risk minimisation measures	IV Iron		Study 57		1	
Pubmed	[216]	Reported Severe Hypersensitivity Reactions after Intravenous Iron Administration in the European Economic Area (EEA) Before and After Implementation of Risk Minimization Measures.	IV Iron		Du_Study 57		1	
EU PAS	[217]	Ivabradine Drug Utilisation Study in Select European Countries: A Multinational, Retrospective, Observational Study to Assess Effectiveness of Risk-Minimisation Measures	Ivabradine	Procoralan	Study 58		1	
ISPE Abstract	[160]	450 | Ivabradine drug utilization study in five European countries: A pass to assess effectiveness of risk minimization measures	Ivabradine	Procoralan	Du_Study 58		1	
EU PAS	[218]	Protocol for the Effectiveness Check of the Awareness and Knowledge of Educational Materials for the Eligard Risk Minimization Program	leuprorelin	Eligard	ongoing	1		
EU PAS	[219]	Global Lomitapide (Juxtapid and Lojuxta) Pregnancy Exposure Registry	lomitapide		ongoing		1	
EU PAS	[220]	LOWER: Lomitapide (Juxtapid and Lojuxta) Observational Worldwide Evaluation Registry	lomitapide	Juxtapid y Lojuxta	ongoing		1	
EU PAS	[97]	Evaluation of the effectiveness of Penthrox® (methoxyflurane) educational tools adopted as additional risk minimisation measures: Healthcare professional and Patient Survey.	methoxyflurane	Penthrox	**ongoing**	1		Obj 3
EU PAS	[96]	Post Authorisation Safety Study (PASS) to evaluate the Risks of Hepatotoxicity and Nephrotoxicity from administration of Methoxyflurane (Penthrox®) for Pain Relief in Hospital Accident & Emergency Departments in the United Kingdom.	methoxyflurane	Penthrox	**ongoing**		1	Obj 3
EU PAS	[153]	Survey to Measure the effectiveness of the Mycamine Prescriber Checklist in the European Union	micafungim	Mycamine	**Study 24**	1		Obj 1, Obj 2
EU PAS	[221]	Drug utilization study of mirabegron (Betmiga®) using real-world healthcare databases from the Netherlands, Spain, United Kingdom and Finland	mirabegron	Betmiga	Study 59		1	
ISPE Abstract	[160]	951 | Risk minimization effectiveness for Mirabegron in the Netherlands, Spain, UK and Finland	mirabegron	Betmiga	Du_Study 59		1	
EU PAS	[222]	Program to evaluate the Tasigna (nilotinib) educational materials: survey to patients and physicians in five EU countries	nilotinib	Tasigna	Study 34	1		
EU PAS	[223]	Use of Intravitreal JETREA® in Clinical Practice: A European Prospective Drug Utilisation Study	ocriplasmin	Jetrea	**Study 41**	1		Obj 2
EU PAS	[224]	An Observational Study to Assess the Effectiveness of the Neulasta® Patient Alert Card and to Measure Medication Errors Related to the Use of the Neulasta® On-Body Injector (20170701)	pegfilgrastim	Neulasta	ongoing	1		
EU PAS	[225]	A PHARMO Study on the Utilization of Pioglitazone in Clinical Practice in The Netherlands with Regard to Diabetic Treatment Regimen and Co-morbidities	pioglitazone		Study 69		1	
EU PAS	[226]	A study on the utilization of pioglitazone in clinical practice in the UK after the label change in July 2011	pioglitazone		Study 70		1	
EU PAS	[227]	A Study on the Utilization of Pioglitazone in Clinical Practice With Regard to Diabetic Treatment Regimen and Comorbidities	pioglitazone		Study 71		1	
EU PAS	[228]	Assessment of Utilisation of Pioglitazone in Denmark Post Label Change (July 2011)	pioglitazone		Study 72		1	
ISPE Abstract		211. Post-Authorisation Safety Study of Pioglitazone Use in Denmark Post Label Change	pioglitazone		Du_Study 72		1	
EU PAS	[229]	Monitoring the effectiveness of risk minimisation in patients treated with pioglitazone-containing products	pioglitazone		Study 73		1	
EU PAS	[146]	Effectiveness evaluation survey for Eurartesim	piperaquine / artenimol	Eurartesim	**Study 11**	1		Obj 1, Obj 2
EU PAS	[230]	Assessment of the effectiveness of risk minimisation measures set up for new safety information for Efient® (Prasugrel): a multinational survey among physicians to evaluate	prasugrel	Efient	**Study 29**	1		Obj 2

Fuente	Ref	Title / link	Drug name	Brand	Study Status	Process indicators	Behavioural or Health/Safety Outcomes	Thesis Objective
		their knowledge and consideration of the new safety warning for Prasugrel in four European countries						
EU PAS	[231]	Assessment of physician behaviour regarding metabolic monitoring of patients treated with SEROQUEL® (quetiapine fumarate) Tablets and SEROQUEL® (quetiapine fumarate) Extended-Release Tablets in selected countries in the European Union (EU)	quetiapine	Seroquel	**Study 2**	1		Obj 1, Obj 2, Obj 3
Pubmed	[232]	Effectiveness of a risk-minimization activity involving physician education on metabolic monitoring of patients receiving quetiapine: results from two post-authorization safety studies.	quetiapine	Seroquel	Du_Study 2	1		
EU PAS	[233]	An observational study to assess the impact of educational material on the metabolic monitoring of patients treated with quetiapine fumarate in Croatia	quetiapine	Seroquel	ongoing		1	
EU PAS	[72]	Objective assessment of metabolic monitoring in patients treated with Seroquel® or Seroquel® XR/quetiapine fumarate: use of IMS Disease Analyzer to assess physician behaviour in the UK and Germany	quetiapine	Seroquel	Study 60		1	Obj 3
EU PAS	[141]	PRJ2250: Survey of prescriber understanding of risks associated with TROBALT	retigabine	Trobalt	**Study 6**	1		Obj 1, Obj 2
EU PAS	[140]	WEUKBRE5744: European Survey of Patient and Prescriber Understanding of Risks Associated with TROBALT™	retigabine	Trobalt	**Study 5**	1		Obj 1, Obj 2
Pubmed	[234]	Survey of Physicians' Understanding of Specific Risks Associated with Retigabine.	retigabine	Trobalt	Du_Study 5 / Study 6	1		
EU PAS	[235]	Impact of EU label changes and revised pregnancy prevention programme for oral retinoid containing medicinal products: utilization and prescribing trends	retinoids		ongoing		1	
EU PAS	[88]	Mabthera Drug Utilisation Study and Patient Alert Card Evaluation in Non-Oncology Patients in Europe: An infusion Centre Based Approach	rituximab	Mabthera	**Study 26**	1	1	Obj 2, Obj 3
Publication	[70]	Additional Risk Minimisation Measures for Medicinal Products in the European Union: A Review of the Implementation and Effectiveness of Measures in the United Kingdom by One Marketing Authorisation Holder	rituximab	MabThera	Du_Study 26			
EU PAS	[236]	Xarelto (Rivaroxaban) Risk Minimisation Plan Evaluation: Patient and Physician Knowledge of Key Safety Messages	rivaroxaban	Xarelto	**Study 42**	1		Obj 2
ISPE Abstract	[158]	9. Evaluating Patient Knowledge of Risks and Safe Use of Xarelto (Rivaroxaban)	rivaroxaban	Xarelto	Du_Study 42	1		
ISPE Abstract	[158]	493. Evaluating Physician Knowledge of Risks and Safe Use of Xarelto (Rivaroxaban)	rivaroxaban	Xarelto	Du_Study 42	1		
EU PAS	[92]	A drug utilisation study in patients treated with EXELON®/PROMETAX® (rivastigmine) transdermal patch	rivastigmine	Exelon / Prometa	**Study 43**	1	1	Obj 2
EU PAS	[237]	A cross-sectional study of patients with immune thrombocytopenic purpura and caregivers to estimate the proportion who administer romiplostim correctly after receipt of home administration training materials (20120269)	romiplostim	Nplate	Study 61		1	
ISPE Abstract	[167]	1004. Assessment of Romiplostim Self- Administration After Receipt of Home Administration Training (HAT) Materials: A Cross-Sectional Study of Patients with Immune Thrombocytopenic Purpura (ITP) and Caregivers	romiplostim	Nplate	Du_Study 61			
Pubmed	[238]	Assessment of Self-Administration of Romiplostim in Patients with Immune Thrombocytopenic Purpura after Receipt of Home Administration Training Materials: a Cross-Sectional Study.	romiplostim	Nplate	Du_Study 61			
EU PAS	[239]	Impact of risk minimisation in patients treated with rosiglitazone-containing products	rosiglitazone		Study 62		1	
EU PAS	[240]	Post-authorisation safety study (PASS) to evaluate risk minimisation measures for medication errors with Uptravi during the titration phase in patients with pulmonary arterial hypertension (PAH) in clinical practice	selexipag	Uptravi	ongoing	1		
EU PAS	[241]	Survey of pharmacists to evaluate the effectiveness of the Viagra Connect national additional Risk Minimisation Measure (aRMM) in the United Kingdom (UK)	sildenafil	Viagra	**Study 44**	1		Obj 2
EU PAS	[242]	XYREM EU-RMP: Effectiveness Assessment Protocol of Educational Materials	sodium oxybate	Xyrem	Study 36	1		
EU PAS	[152]	Observational, Cross-Sectional Post-Authorisation Safety Study to Assess Healthcare Provider Awareness of Risks Related to Sofosbuvir and Ledipasvir/Sofosbuvir	sofosbuvir and ledipasvir/sofosbuvir	Harvoni	**Study 21**	1		Obj 1, Obj 2

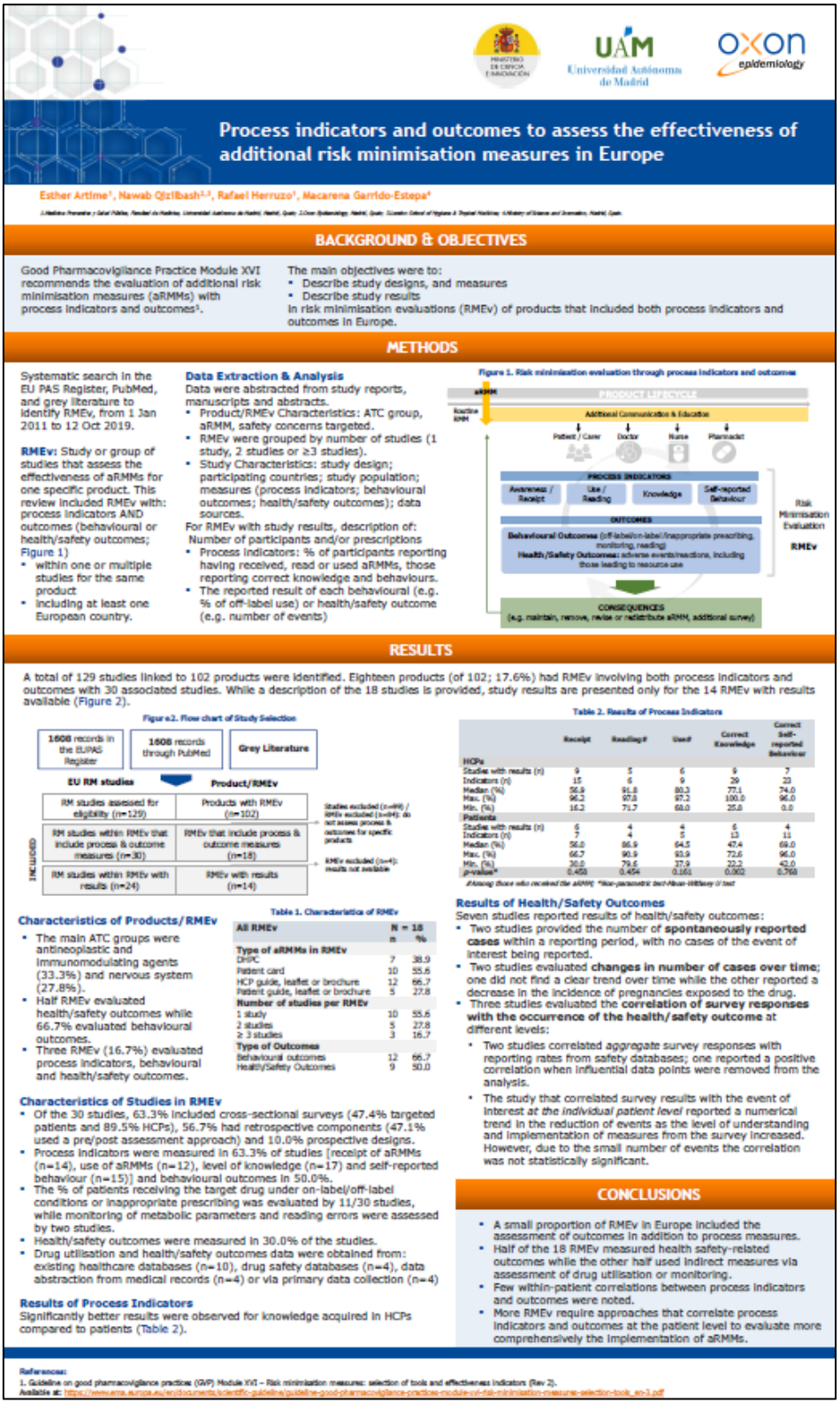
Fuente	Ref	Title / link	Drug name	Brand	Study Status	Process indicators	Behavioural or Health/Safety Outcomes	Thesis Objective
EU PAS	[243]	European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance	strontium ranelate	Protelos	Study 63		1	
ISPE Abstract	[244]	408 | Impact of risk minimisation measures on the use of strontium ranelate: A multinational cohort study in 5 EU countries by the EU-ADR Alliance	strontium ranelate	Protelos	Du_Study 63		1	
ISPE Abstract	[167]	799. Impact of Risk Minimisation Measures on the Use of Strontium Ranelate: A Multi-National Cohort Study in 5 EU Countries by the EU-ADR Alliance	strontium ranelate	Protelos	Du_Study 63		1	
ISPE Abstract	[167]	8. The Impact Of Risk Minimisation Measures On The Incidence And Prevalence Of Use Of Strontium Ranelate At The Population Level: Preliminary Results Of A Multi-National Cohort Study Including 5 European Countries	strontium ranelate	Protelos	Du_Study 63		1	
EU PAS	[245]	Evaluation of the Effectiveness of Risk Minimisation Measures: A Survey among Health Care Professionals to Assess their Knowledge on Dosing and Administration of Obizur® (Susoctocog alfa) in 6 European Countries	susoctocog alfa	Obizur	ongoing	1		
EU PAS	[246]	A Post-Authorization Safety Study of the Use of Intravenous Telavancin (VIBATIV®) in the Clinical Setting	telavancin	Vivatib	ongoing		1	
EU PAS	[247]	An Observational, Drug Utilization Study of Viread® in Children and Adolescents with HIV-1 Infection	tenofovir	Viread	Study 64		1	
EU PAS	[248]	Viread Observational, Cross -Sectional Drug Utilisation Study in Children and Adolescents with Chronic Hepatitis B	tenofovir	Viread	Study 65		1	
EU PAS	[99]	Drug Utilization Study of Thiocolchicoside (TCC) containing medicinal products for systemic	thiocolchicoside		**ongoing**		1	Obj 3
EU PAS	[249]	Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Thiocolchicoside containing Medicinal Products for Systemic Use in France, Greece, Italy and Portugal	thiocolchicoside		**Study 27**	1		Obj 2, Obj 3
ISPE Abstract	[160]	960 | Evaluation of the effectiveness of risk minimisation measures targeting physicians on prescribing practices of thiocolchicoside containing medicinal products for systemic use	thiocolchicoside		Du_Study 27	1		
Google	[249]	https://www.omicsonline.org/open-access/evaluation-of-the-effectiveness-of-risk-minimisation-measures-targeting-physicians-on-prescribing-practices-of-thiocolchicoside-co-2161-1165-1000372-108159.html	thiocolchicoside		Du_Study 27	1		
Publication	[70]	Additional Risk Minimisation Measures for Medicinal Products in the European Union: A Review of the Implementation and Effectiveness of Measures in the United Kingdom by One Marketing Authorisation Holder	trastuzumab	Kadcyla	**Study 81**	1	1	Obj 2, Obj 3
EU PAS	[80]	Drug utilisation study, in five European countries, using cross sectional analysis, to assess the extent of prescriptions of trimetazidine for its withdrawn ophthalmological and ENT indications among general practitioners, ophthalmologists and ENT specialists	trimetazidine		**Study 66**		1	Obj 3
EU PAS	[79]	Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey among Health Care Professionals to Assess their Knowledge and Attitudes on Prescribing Conditions of Trimetazidine in Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain	trimetazidine		**Study 18**	1		Obj 1, Obj 2, Obj 3
Pubmed	[250]	Evaluation of the effectiveness of risk minimization measures for trimetazidine: A cross sectional joint PASS survey among physicians in selected European countries.	trimetazidine		Du_Study 18	1		
EU PAS	[81]	Evaluation of the Effectiveness of Risk Minimization Measures: Trimetazidine Drug Utilization Study in European Countries using databases – analysis for France, Hungary, Romania and Spain	trimetazidine		**Study 67**		1	Obj 3
Pubmed	[251]	A drug utilization study to evaluate effectiveness of risk minimization measures for trimetazidine in France, Hungary, Romania and Spain.	trimetazidine		Du_Study 67		1	
EU PAS	[252]	Non-interventional post-authorization safety study to describe use by indication and clinical outcomes among patients with complicated intra-abdominal infection or complicated skin and soft tissue infection treated with tigecycline (tygacil®) in the European union	tygeciclina	Tygacil	Study 68		1	
EU PAS	[90]	A Joint Drug Utilisation Study (DUS) of valproate and related substances, in Europe, using databases	valproate		**Study 87**		1	Obj 3
EU PAS	[89]	Evaluation of the Effectiveness of Risk Minimisation Measures: A Joint PASS Survey and Drug Utilisation Study among Health Care Professionals to Assess their Knowledge and Attitudes	valproate		**Study 28**	1		Obj 2, Obj 3

Fuente	Ref	Title / link	Drug name	Brand	Study Status	Process indicators	Behavioural or Health/Safety Outcomes	Thesis Objective
		on Prescribing Conditions of valproate in France, Germany, Spain, Sweden and United Kingdom						
ISPE Abstract	[158]	533. Usage Of Valproate In Women In The UK	valproate		**Study 76**		1	Obj 3
ISPE Abstract	[244]	834 | Utilising the CPRD pregnancy register to examine the pattern of antiepileptic drug use during pregnancy in the United Kingdom	valproate		Du_Study 76		1	
EU PAS	[253]	An assessment of physician knowledge and understanding of the risks of vandetanib (Caprelsa®) within the European Union.	vandetanib	Caprelsa	**Study 38**	1		Obj 2
Publication	[70]	Additional Risk Minimisation Measures for Medicinal Products in the European Union: A Review of the Implementation and Effectiveness of Measures in the United Kingdom by One Marketing Authorisation Holder	vismodebig	Erivedge	**Study 80**	1	1	Obj 2, Obj 3
Pubmed	[254]	Relevance of a "Dear Doctor letter" to alert healthcare providers to new recommendations for vitamin D administration.	vitamin D		Study 30*	1		
EU PAS	[138]	Evaluation of the effectiveness of additional risk minimisation measures (aRMMs) that aim to reduce the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in the European Union (EU)	voriconazole	Vfend	**Study 1**	1		Obj 1, Obj 2
ISPE Abstract	[167]	705. Evaluating the Effectiveness of Additional Risk Minimisation Measures (aRMM) for Voriconazole in 10 European Countries	voriconazole	Vfend	Du_Study 1	1		
Google	[127]	https://link.springer.com/article/10.1007/s40290-019-00273-4	voriconazole	Vfend	Du_Study 1	1		
EU PAS	[255]	E2090-E044-501: A Retrospective database Study of the Prescribing of Zonismaide in UK General Practice: A Drug Utilisation Study as Part of Post-Marketing Safety Surveillance	zonismaide	Zonegran	ongoing		1	
EU PAS	[256]	Evaluating the effectiveness of the revised alli® pack information in helping pharmacy staff within the EU supply alli® appropriately	orlistat	Alli	**Study 32**	1		Obj 2
EU PAS	[144]	EDURANT / EVIPLERA Health Care Professional Survey	rilpivirine emtricitabine tenofovir disoproxil	Edurant / Eviplera	**Study 9**	1		Obj 1, Obj 2
EU PAS	[257]	Evaluation of referring HCPs' and parents'/carers' understanding of specific risks associated with Strimvelis™ treatment	autologous cd34+ enriched cell fraction that contains cd34+ cells transduced with retroviral vector that encodes for the human ada cdna sequence	Strimvelis	ongoing		1	

*Excluded from Objective 2 as considered outside the scope of the review
Studies with Status 'Du_' are duplicates of EU RM studies

15. Annexes

Annex 1.



Process indicators and outcomes to assess the effectiveness of additional risk minimisation measures in Europe

Esther Artime[1], Nawab Qizilbash[2,3], Rafael Herruzo[1], Macarena Garrido-Estepa[4]

BACKGROUND & OBJECTIVES

Good Pharmacovigilance Practice Module XVI recommends the evaluation of additional risk minimisation measures (aRMMs) with process indicators and outcomes[1].

The main objectives were to:
- Describe study designs, and measures
- Describe study results

in risk minimisation evaluations (RMEv) of products that included both process indicators and outcomes in Europe.

METHODS

Systematic search in the EU PAS Register, PubMed, and grey literature to identify RMEv, from 1 Jan 2011 to 12 Oct 2019.

RMEv: Study or group of studies that assess the effectiveness of aRMMs for one specific product. This review included RMEv with: process indicators AND outcomes (behavioural or health/safety outcomes; Figure 1)
- within one or multiple studies for the same product
- including at least one European country.

Data Extraction & Analysis
Data were abstracted from study reports, manuscripts and abstracts.
- Product/RMEv Characteristics: ATC group, aRMM, safety concerns targeted.
- RMEv were grouped by number of studies (1 study, 2 studies or ≥3 studies).
- Study Characteristics: study design; participating countries; study population; measures (process indicators; behavioural outcomes; health/safety outcomes); data sources.

For RMEv with study results, description of: Number of participants and/or prescriptions
- Process indicators: % of participants reporting having received, read or used aRMMs, those reporting correct knowledge and behaviours.
- The reported result of each behavioural (e.g. % of off-label use) or health/safety outcome (e.g. number of events)

Figure 1. Risk minimisation evaluation through process indicators and outcomes

RESULTS

A total of 129 studies linked to 102 products were identified. Eighteen products (of 102; 17.6%) had RMEv involving both process indicators and outcomes with 30 associated studies. While a description of the 18 studies is provided, study results are presented only for the 14 RMEv with results available (Figure 2).

Figure e2. Flow chart of Study Selection

Table 1. Characteristics of RMEv

All RMEv	N = 18 n	%
Type of aRMMs in RMEv		
DHPC	7	38.9
Patient card	10	55.6
HCP guide, leaflet or brochure	12	66.7
Patient guide, leaflet or brochure	5	27.8
Number of studies per RMEv		
1 study	10	55.6
2 studies	5	27.8
≥ 3 studies	3	16.7
Type of Outcomes		
Behavioural outcomes	12	66.7
Health/Safety Outcomes	9	50.0

Characteristics of Products/RMEv
- The main ATC groups were antineoplastic and immunomodulating agents (33.3%) and nervous system (27.8%).
- Half RMEv evaluated health/safety outcomes while 66.7% evaluated behavioural outcomes.
- Three RMEv (16.7%) evaluated process indicators, behavioural and health/safety outcomes.

Characteristics of Studies in RMEv
- Of the 30 studies, 63.3% included cross-sectional surveys (47.4% targeted patients and 89.5% HCPs), 56.7% had retrospective components (47.1% used a pre/post assessment approach) and 10.0% prospective designs.
- Process indicators were measured in 63.3% of studies [receipt of aRMMs (n=14), use of aRMMs (n=12), level of knowledge (n=17) and self-reported behaviour (n=15)] and behavioural outcomes in 50.0%.
- The % of patients receiving the target drug under on-label/off-label conditions or inappropriate prescribing was evaluated by 11/30 studies, while monitoring of metabolic parameters and reading errors were assessed by two studies.
- Health/safety outcomes were measured in 30.0% of the studies.
- Drug utilisation and health/safety outcomes data were obtained from: existing healthcare databases (n=10), drug safety databases (n=4), data abstraction from medical records (n=4) or via primary data collection (n=4)

Results of Process Indicators
Significantly better results were observed for knowledge acquired in HCPs compared to patients (Table 2).

Table 2. Results of Process Indicators

	Receipt	Reading#	Used	Correct Knowledge	Correct Self-reported Behaviour
HCPs					
Studies with results (n)	9	5	6	9	7
Indicators (n)	15	6	9	29	23
Median (%)	86.8	91.8	80.3	77.1	74.0
Max. (%)	96.2	97.0	97.2	100.0	96.0
Min. (%)	16.2	71.7	68.0	25.0	0.0
Patients					
Studies with results (n)	6	4	4	6	4
Indicators (n)	7	4	5	13	11
Median (%)	56.0	86.9	64.5	47.4	69.0
Max. (%)	66.7	90.9	93.9	72.6	96.0
Min. (%)	30.0	79.6	37.9	22.2	42.0
p-value*	0.458	0.454	0.161	0.002	0.768

#Among those who received the aRMM; *Non-parametric Sect-Mann-Whitney U test

Results of Health/Safety Outcomes
Seven studies reported results of health/safety outcomes:
- Two studies provided the number of **spontaneously reported cases** within a reporting period, with no cases of the event of interest being reported.
- Two studies evaluated **changes in number of cases over time**; one did not find a clear trend over time while the other reported a decrease in the incidence of pregnancies exposed to the drug.
- Three studies evaluated the **correlation of survey responses with the occurrence of the health/safety outcome** at different levels:
  - Two studies correlated *aggregate* survey responses with reporting rates from safety databases; one reported a positive correlation when influential data points were removed from the analysis.
  - The study that correlated survey results with the event of interest *at the individual patient level* reported a numerical trend in the reduction of events as the level of understanding and implementation of measures from the survey increased. However, due to the small number of events the correlation was not statistically significant.

CONCLUSIONS
- A small proportion of RMEv in Europe included the assessment of outcomes in addition to process measures.
- Half of the 18 RMEv measured health safety-related outcomes while the other half used indirect measures via assessment of drug utilisation or monitoring.
- Few within-patient correlations between process indicators and outcomes were noted.
- More RMEv require approaches that correlate process indicators and outcomes at the patient level to evaluate more comprehensively the implementation of aRMMs.

References:
1. Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2).
Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-1.pdf

Annex 2.

Participation in Survey Studies of the Effectiveness of Risk Minimisation Measures in Europe

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BACKGROUND AND OBJECTIVES

One main challenge of survey studies assessing the effectiveness of risk minimisation measures (RM Survey studies) is country selection and participant recruitment which may result in selection bias[1–3].

The main objectives were to:
- Describe country selection in EU RM Survey studies
- Describe subject participation in EU RM Survey studies

METHODS

Systematic review using the EU PAS Register, PubMed, and grey literature to identify EU RM Survey studies that assess the effectiveness of risk minimisation measures (RMMs), between 1 January 2011 and 12 October 2019.

Study Inclusion Criteria:

Studies:
- with a cross-sectional survey component assessing the effectiveness of routine or additional RMMs.
- including at least one European country.
- evaluating process indicators, defined as 'measures of the extent of implementation of the original plan, and/or variations in its delivery' e.g. receipt, usage, knowledge, implementation of clinical actions[4].
- with results in the form of final study report (FSR) or manuscript/abstract.

Data Extraction & Analysis

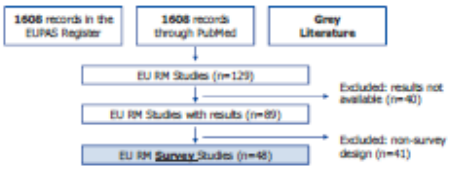
- Data from study results were extracted: 1) target number of countries; 2) number of countries with participants; 3) target population (HCPs, patients/caregivers); 4) target number of participants; 5) invited participants; 6) contacted participants; 7) screened participants; and 8) completers (participant HCPs/patients that completed the survey).
- The following were calculated:
  - Number/% of studies in which each country participated.
  - Number/% of completers that each country provided, by study and overall, 1) as the % by country of completers provided to the overall number of completers in all studies identified; or 2) as the % by country of completers provided to the overall number of completers in studies with that country participation identified.
  - Response rate: % of participants completing the survey among those invited to participate. The range of response rates is provided.

Results are presented for HCP and patient surveys separately.

RESULTS

A total of 129 EU RM Studies were identified (Figure 1). Forty-eight studies had a survey component: 44 were surveys of HCPs and 14 were surveys of patients and/or caregivers.

Figure 1 - Flow chart of Study Selection



HCP Surveys

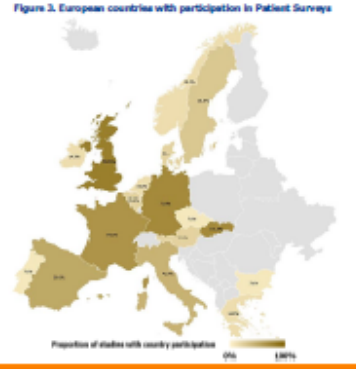
- Twenty-eight European countries were included with an average of 5 (Range: 1 to 18) countries targeted per survey.
- The total number of HCP participants was 18207 HCPs; 17502 with country-specific participation data.
- The highest recruiting countries were (Figure 2): the UK (33/44), Spain (28/44), France (29/44) and Germany (29/44), contributing 64.2% (by country range: 17.8% to 12.7%) of all participants with country-specific data.
- Italy, Sweden, Denmark, Netherlands, Belgium, and Austria participated in 18, 17, 15, 11, 10 and 10 surveys, respectively, recruiting 21.5% (Range: 2.0% to 6.3%) of all participants.
- The remaining 18 countries participated in 1 to 9 studies and provided 14.3% (Ranging from 0% to 2.5%) of participants.
- The median HCP response rate by country ranged from 0.3% to 22.0%, being highest in Greece (22.0%), Italy (18.7%) and Czech Republic (18.4%).

Figure 2. European countries with participation in HCP Surveys

Patient Surveys

- 17 different countries were involved with an average of 5.0 (Range: 3 to 10) countries participating per survey.
- One survey also included caregivers.
- The total number of patient/caregiver participants was 4129; 2996 with country-specific participation data.
- The UK (11/14), Germany (10/14), France (9/14) and Spain (7/14) were also the top recruiters in the 14 patient surveys (Figure 3), recruiting 65.7% of all participants with country-specific data.
- The median patient response rate by country ranged from 10.0% to 90.3%, being highest in Spain (90.3%) and Germany (78.9%).

Figure 3. European countries with participation in Patient Surveys



CONCLUSIONS

- Some countries are overrepresented in HCP and patient EU RM survey studies.
- Subject participation remains low, especially for patient surveys.
- Strengthened recommendations to guide country selection and participation are warranted.

References:
1. ENPE Whitepaper -Evaluating the Effectiveness of Additional Risk Minimisation Measures via Surveys in Europe: Challenges and Recommendations. 2016. Available at: https://pharmacoepi.org/pub/?id=1969326F-0e69-11e7-9f74-f23bd7be865f
2. Artime E, Qizilbash N, Garrido-Estepa M, Vora P, Soriano-Gabarró M, Ballarin A, et al. Are risk minimization measures for approved drugs in Europe effective? A systematic review. Expert Opin Drug Saf. 2019;18:443–54.
3. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 8). EMA/95098/2010. Available at https://www.encepp.eu/standards_and_guidance
4. Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-

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